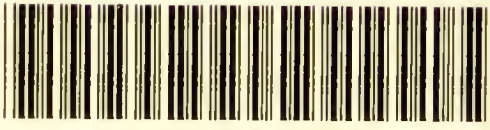

CLINICAL LECTURES

ON

URINE.

BY

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PREFACE.

THE following Lectures were delivered at University College Hospital during the winter of 1896. They were reported at the time of their delivery, and they are now published with only a few verbal corrections. This must be my excuse both for their conversational style and also for their incompleteness in many respects.

J. ROSE BRADFORD.

November, 1897.

CLINICAL LECTURES

ON

URINE.

No. I.

THERE are but few diseases which do not alter in some way the composition of the urine, and there are several diseases which can only be diagnosed by an examination of the urine,—thus diabetes mellitus may be overlooked unless the urine is examined as a routine measure, and in the same way a contracted or granular kidney may be overlooked. As regards the examination, though much that is recommended is more applicable to hospital than private practice, still as near an approach to hospital practice as possible should at any rate be attempted. The first rule, especially in insurance cases for instance, is that you ought to see the patient pass the urine yourself. In making your patient pass the urine for examination you should follow the rule of the surgeons and cause it to be passed in two portions, one small quantity first to wash out the urethra, and then a larger quantity; this is more especially necessary

when the urine contains pus or blood. In women it is frequently necessary to pass a catheter in order to make certain whether pus cells, blood, &c., come from the urinary tract or not. The use of the catheter may be necessary in the male in cases of supposed malingering. In many diseases it is absolutely necessary to take the whole twenty-four hours' urine and to mix it up. I am perfectly well aware that it is very difficult to do this in private practice, but it is well to try and obtain this. It is important in several renal diseases, for example diabetes; in granular kidneys it is of consequence because of the determination of the specific gravity. Plenty of people may pass urine of 1005 specific gravity temporarily, but a specific gravity of even 1010 for the whole twenty-four hours' urine would be very abnormal. Hence you should be very careful to examine a sample of the whole twenty-four hours, and not a particular sample that the patient may bring you at the time you see him. There is another important point to attend to in this matter, and that is to obtain if possible a specimen of the starving urine—the urine passed before breakfast,— and also another specimen of the urine passed two or three hours after the heaviest meal of the day, lunch or dinner, as the case may be. This is important, for instance, in some cases of gravel, because in such patients the gravel tends to deposit in the morning urine before breakfast, and in some cases of albuminuria and glycosuria, the

abnormal substances are found only after meals. For an ideal examination of the urine you should have, then, the whole amount passed during the twenty-four hours mixed up, and take a sample of that; you should take a sample of the starving urine and one also of the urine passed after the heaviest meal of the day. If you wish to make perfectly certain that albumen and sugar are not in the urine, this plan must be adopted.

In disease the urine may undergo qualitative or quantitative changes, or both. It is commonly stated that the average quantity of urine passed in the twenty-four hours is some fifty ounces, and that it varies from a minimum of twenty ounces to a maximum of eighty ounces. A more important clinical point is that the amount of water lost is about 50 per cent. of the fluid taken in; that is to say, four to five pints is the usual amount for an adult to take in the day. I am not going into the question of the physiology of the urinary secretion, but I would say in reference to the water of the urine that it depends practically upon the rate of the blood-flow through the kidneys, and upon the activity of the glomerular epithelium, and these are the proximate causes of all variations in the amount of the urine. But more important from a clinical point of view are the other ultimate factors on which the amount depends. Firstly, the quantity of water passed in the urine depends on the amount of fluid taken in; secondly, it depends on the amount of fluid that is lost by other channels,

and more particularly by the skin, the lungs, and the bowels. In health, the amount of fluid in the tissues remains pretty constant, so that variations in the amount of fluid in the tissues do not appreciably affect the amount of urine in health. In disease, however, great variations occur in the amount of fluid in the tissues, and therefore you have in addition to the loss by the lungs, the skin, and the bowels, to take into account the varying amount of fluid in the tissues. If a patient becomes dropsical the amount of urine necessarily diminishes, and the variations in the amount of dropsy (which is a condition in which there is excess of fluid in the tissues) must necessarily affect the urine, even if the dropsy is not dependent upon renal disease. In the case of a patient with heart disease a sudden diminution in the amount of urine by no means indicates necessarily the onset of grave renal disease, it may point to the onset of dropsy. The quantity of urine depends, then, on the rate of the flow of the blood through the kidneys and the activity of the glomerular epithelium, and beyond this there are the questions of the amount of fluid ingested, and the amount lost by other channels, and the presence or absence of dropsy.

In disease the quantity of urine may be increased or diminished. Most diseases tend to diminish the quantity of urine, but there are some diseases in which the quantity of urine is increased. The increase in the quantity of urine may be temporary

or more or less permanent. There are various conditions which will cause a temporary increase in the flow of urine quite apart of course from copious drinking, which is of course the most obvious cause; it is asserted that in excessive drinking you may have the specific gravity of the urine lowered to one comparable to that of water. A milk diet, containing as it does a diuretic like lactose, will lead to the excretion of a copious dilute urine. A temporary increase in the amount of the urinary water occurs on the subsidence of nervous paroxysms, *e. g.* after epileptic and hysterical attacks, and after asthma. Other instances are those in which there is a subsidence of dropsy, and the subsidence will often show itself at first rather in an increased quantity of the urine than by any notable diminution in the amount of the dropsy. Patients with chronic Bright's disease passing an increased amount of urine are sometimes thought to be going on to the stage of cirrhotic kidney, when the increased flow is often due to a diminution in the amount or disappearance of the dropsy. A temporary increase in the flow of urine is seen as a result of the re-establishment of the urinary secretion after the flow has been obstructed. Thus in renal colic, after the calculus has passed, the patient passes much urine of a very dilute character. A temporary increase in the flow of urine is also seen during the subsidence of acute and subacute inflammation of the kidney. In many diseases like diabetes mellitus and diabetes

insipidus, renal cirrhosis, and other diseases of the kidney, the quantity of urine is permanently increased. In all these conditions the quantity of urine is permanently increased as long as the disease lasts. In diabetes mellitus and in diabetes insipidus the quantity of urine is greatly increased, but the increase is usually greater in diabetes insipidus than in diabetes mellitus. In diabetes insipidus the patient may pass any quantity from ten to twenty pints, and one case is recorded in which thirty pints were passed in the day; whereas in diabetes mellitus the quantity of 150 to 200 ounces is rarely exceeded. These diseases are classified as causing a permanent increase in the urine, but in both the increased flow may stop suddenly, and more especially in diabetes insipidus. In diabetes insipidus the urine is like water, quite clear, with a low specific gravity, whereas in the other form the specific gravity of the urine is as a rule high.

In certain forms of Bright's disease the quantity of urine is greatly increased, and in all forms of acute Bright's disease a temporary increase in the amount is seen during the subsidence of the dropsy. In chronic Bright's disease the flow is often increased, provided the patient is not dropsical. In renal cirrhosis the quantity of urine passed is considerable, 80 to 100 ounces. In the above-mentioned cases of Bright's disease about 60 ounces would be an average, that is to say, a little above the normal; but in the granular kidneys the

quantity is considerably above the normal, but rarely above 100 ounces. Certain forms of chronic Bright's disease may produce a greater increase in the urinary flow, this form is readily diagnosed, because the quantity of albumen present is considerable ; in the granular kidney the urine does not always contain albumen, and a granular kidney may occasionally cause death without producing albumen in the urine.

The quantity of urine passed may be diminished, and the flow may be suppressed. It is customary to describe two forms of suppression, one obstructive suppression, and the other non-obstructive suppression. In obstructive suppression the suppression of the urine is caused by an obstruction to the flow of urine along the ureters. The urine may be pent up behind the obstruction, or there may be actual suppression, with no urine in the renal pelvis. These cases of obstructive suppression may, therefore, be divided into two groups; in the one the ureters and renal pelvis are dilated and distended with urine; in the other, notwithstanding the obstruction, there is little or no distension of the urinary channels. Cancer of the uterus frequently involves the ureters, and under these circumstances the ureters may be distended to the size of the index finger. One of the most frequent causes of obstructive suppression is the impaction of a stone in a ureter, when the other kidney is either absent or destroyed by previous disease. Obstructive suppression is a condition

that can go on for a considerable time, and it is usually stated that it may go on for from eight to ten days. The most remarkable thing about it is that the patients are not very ill, they do not feel very ill, nor do they look very ill on casual examination. Such patients are not very ill till very shortly before their death, and they often die suddenly, and the mind may remain clear until the last. The only signs that point towards the dangerous condition of these patients are, that the pupils become contracted, the patient's temperature steadily falls, so that they have a temperature of 96° or 95°, and then just before the end they may have muscular twitches. But the main point is that in these cases of so-called obstructive suppression, where there is a mechanical obstruction, they do not suffer from what is called uræmia; they die quite suddenly, usually about the middle of the second week, and during the whole illness they may be in complete possession of their faculties, without any serious symptoms of any kind.

Non-obstructive suppression is a very serious malady indeed, and is met with in a variety of conditions; it is a condition in which there is complete and generally fatal suppression, without there being any mechanical impediment to the exit of the urine. It may occur in people with perfectly healthy kidneys as a result of various operative procedures. When I say a perfectly healthy kidney I mean they do not show any signs of gross disease. Non-obstructive suppression of

urine may occur from passing a catheter; it is not very uncommon for this to occur when there is serious disease of the kidneys. Complete suppression may also occur as a result of various abdominal injuries and diseases, and also sometimes as a sequel to operations. Exploratory operations on the kidneys are very liable to lead to suppression and uræmia if these organs are diseased. Fatal suppression has occurred more than once in cases where the kidney has been cut down upon for stone, and where there was in addition chronic Bright's disease or waxy disease; and I have heard of a case where fatal suppression followed nephrectomy, and where the kidneys showed no gross lesion post mortem.

Non-obstructive suppression with apparently healthy kidneys is seen sometimes in various serious abdominal diseases. In one case a patient with perforation of the duodenum died not from the peritonitis,—he was walking about the ward,—but from suppression of urine. Recently there was a case of a woman who after an abortion died from suppression of urine. There was no peritonitis, and the uterus showed no signs of disease, and the kidneys showed no gross lesions although they may have been slightly fatty. As a result of severe abdominal injuries suppression is not uncommon. The next variety of non-obstructive suppression is that occurring in diphtheria. Here the mechanism is not certainly known, but it is probable that it occurs as the result of the

action of the toxins produced in diphtheria on the renal epithelium.

A familiar form of complete suppression is that seen as a result of very severe congestion, active or passive, of the kidneys. Very acute nephritis produced by scarlet fever may cause suppression of urine, and this is different to the suppression occurring in diphtheria, in that the latter disease does not cause the gross lesions in the kidneys seen as a result of scarlet fever. In scarlet fever there are obvious changes, and in some cases the congestion has been so extreme that the capsule of the kidney has been ruptured. In the passive congestion of the kidneys due to thrombosis of the renal veins, complete suppression may occur, but the thrombosis is often unilateral, and then suppression does not occur. Suppression sometimes occurs as a result of acute congestion produced by poisons, and there was a case recorded a few months ago in which a woman got severe suppression from the application of a very large blister.

Non-obstructive suppression is very rapidly fatal; the patients usually die in two to three days, with very severe vomiting, and headache, convulsions, and coma—that is to say, the clinical picture of certain forms of uræmia.

Diminution in the flow of urine is seen under a variety of conditions; first of all, it will occur if large quantities of water are lost from other channels. Thus in febrile diseases the hurried respirations, the sweating will lead

to an increased loss of water from the lungs and skin, and thus the urinary flow is diminished, and a typical instance of this is seen in pneumonia. In any disease in which diarrhœa is a marked symptom there may be a considerable diminution in the quantity of urine, and if the diarrhœa is very severe, complete suppression may occur. Then, as mentioned above, the presence of dropsy will diminish the flow of urine, and this whether the diminution in the flow of the urine is the cause of the dropsy, or the onset of the dropsy is the cause of the diminution of the flow; but the fact remains that they vary inversely, there is a relation between the two of such a character that the fluctuations in the quantity of urine will very often give more reliable information of the subsidence of the dropsy than any physical signs. Anything which diminishes the rate of the blood flow through the kidney, and more particularly venous congestion, will produce diminution in the flow of the urine; thus a scanty secretion of urine occurs as the result of abdominal tumours, collections of fluid in the abdomen, and in heart and lung disease, and so forth. In all these the quantity of urine is greatly decreased, owing to the passive congestion of the kidney. In these conditions the quantity is usually not diminished to much under twenty ounces. Diminution in the flow of urine may also occur in diseases involving and destroying the secreting structures of the kidney, the typical instance is chronic Bright's disease with

dropsy; but in many diseases destroying the renal tissues a more or less abundant dilute urine is passed.

The *specific gravity* of the normal urine may vary from 1015 to 1025, and in disease the specific gravity may approximate to that of water, or rise as high as 1060. An abnormally low specific gravity is usually a sign of serious disease if it is a permanent condition, and if it is found in the whole of the twenty-four hours' urine. Urine of low specific gravity is secreted after copious drinking, and in the conditions described above, where there is a temporary increase in the urinary flow; but a permanent lowering means usually some serious kidney lesion, such as granular kidneys, waxy disease, &c., unless it is due to diabetes insipidus. As regards the increase in specific gravity it is of little importance, except in the case of diabetes mellitus. All concentrated urines have a high specific gravity. One of the most important points about diabetes is that occasionally in this disease there is a low specific gravity, and yet there may be a considerable amount of sugar present, even with the specific gravity as low as 1010. In diabetes the specific gravity and the percentage amount of sugar do not necessarily vary together. Supposing two samples of diabetic urine, one of 1040 specific gravity and one of 1045, it does not follow that the higher specific gravity indicates the greater amount of sugar. In diabetes mellitus there is a great increase in the amount of

urea in the urine; but if the patient is passing large quantities of urine, then the specific gravity does vary with the amount of sugar present, because the other urinary constituents are present in comparatively such small amounts that the sugar is the most abundant urinary constituent. If a patient with diabetes only passes very small quantities of urine the specific gravity is very much affected by the other constituents present; if the patient passes large quantities, then the other urinary constituents are scanty, and the specific gravity does vary with the sugar.

No. II.

Albuminuria.—By the term albuminuria is meant the presence of proteid matter in the urine, but not necessarily the presence of albumin. The first question that presents itself is whether proteid matter is present in the normal urine,—whether there is such a thing as physiological albuminuria. That depends largely on the definition of a normal urine, but apparently 30 per cent. at the very lowest estimate, of apparently healthy people, have some variety of albumen in the urine. The amount present is usually small, and is often not recognisable except by special methods of investigation. There are two ways of looking at physiological albuminuria; one that it is a normal occurrence, and the other is that these patients are really on the borderland between health and disease. It has not been clearly established that cases of so-called physiological albuminuria necessarily go on to organic disease of the kidneys, and to permanent albuminuria. The great point is that there are some 30 per cent. of persons who have no marked symptoms of any disease except the presence of this small quantity of albumen in the urine. In some of the cases the patients have traces of albumen in the urine always, but the

greater majority have only albumen in the urine under certain circumstances,—as, for instance, after severe exercise pushed to the point of great fatigue. This accounts for one group of cases. A second group consists of those cases where albumen is only present after meals; and a third group is where albumen is found in the urine passed some two to three hours after getting up in the morning, the so-called postural albuminuria. There is another class, a fourth group of slight importance, in which albumen is said to appear in the urine after bathing. But this last group is of but little interest. The important groups are those in which albumen appears in the urine after meals, after severe exercise, and in the morning. In some cases the albuminuria appears with such remarkable diurnal constancy as to merit the term cyclical albuminuria.

To consider the albumen which appears after meals; there are certain articles of diet that will produce albuminuria in any person, provided only that enough is taken; for instance, raw eggs will produce albuminuria practically in 100 per cent. of persons. Half a dozen raw eggs will produce albuminuria in almost anyone, and when people are ill it is not an uncommon thing for raw eggs to be taken in considerable quantity; it is worth remembering that albuminuria may occasionally be dependent on the diet that is ordered. Ordinary diet is followed by albuminuria in a considerable number of apparently healthy people, and

more particularly in young men, or rather boys. In these cases small quantities of albumen are usually to be noticed two to three hours after the heavy meals of the day. In cases of dietetic albuminuria, and in the albuminuria seen after severe exercise, hyaline casts are frequently found in the urine after centrifugalising, and hence the presence of these casts does not necessarily mean that there is any permanent structural disease of the kidney. There is a particular variety of this so-called functional albuminuria spoken of as cyclical albuminuria, and sometimes known also as Pavy's disease, in which you cannot trace that the albuminuria is dependent on diet or exercise. In these cases of cyclical albuminuria the albumen appears in the urine at more or less regular intervals; thus it may be seen either in the morning or in the evening, but not in between times. These cases of cyclical abbuminuria are mainly seen in young persons, and more especially in boys, and it is not an uncommon thing to find patients between fifteen and twenty years of age with a considerable quantity of albumen in the urine. Before, however, the diagnosis of dietetic, cyclical, or functional albuminuria is made, you ought to be very careful to centrifugalise the urine, and to examine the deposits for casts. You must be on the watch for the presence of spermatozoa, as some cases of albuminuria are due to masturbation, and if you detect the presence of spermatozoa in the urine it will give you a clue to the nature of

the cause. Therefore you should not make a definite diagnosis until the urine has been centrifugalised and the deposit examined. It is necessary to centrifugalise the urine, because by simply allowing the urine to stand you do not get enough deposit for your examination. Another reason for centrifugalising the urine is that there is a form of granular kidney in which the albuminuria may be remarkably inconstant, and the mistake of diagnosing a trivial condition, such as functional albuminuria, when there is really a very serious state of things present, *e. g.* granular kidney, may be made, and this mistake may often be avoided by finding definite renal elements in the deposit obtained after centrifugalisation of the urine.

The amount of albumen which is present in these cases of functional albuminuria is often so small as not to be detected by the nitric acid test; that test only yields evidence of albumen in about 10 per cent. instead of 30 per cent. of apparently healthy persons. The picric acid test or some other equally delicate reaction must be used. The amount of albumen is very variable, but usually there is only a trace present. Occasionally, however, larger amounts are present, as, for instance, one tenth, and I have seen a case where there was as much as one sixth, and yet no signs of organic disease were present.

We will pass on now to pathological albuminuria. Albuminuria is brought about, strictly speaking, in only one way, and that is if the epithelial structures

of the kidney are damaged, and more especially the glomerular epithelium. Damage to the glomerular epithelium may be brought about in a great variety of ways, and consequently, for clinical purposes, it is convenient to classify albuminuria as dependent on several causes, although as a matter of fact albuminuria is probably always due to a change of some kind in the renal epithelium. The first variety of albuminuria recognised is the albuminuria dependent on changes in the composition of the blood,—so-called blood albuminuria. A typical example of this albuminuria is that which occurs in empyema, or in any case in which there is a large collection of pus in some part of the body. Albumen occurs in the urine in these cases because the pus in the chest, &c., contains a considerable amount of albumoses; these are excreted by the kidney, and in being excreted they damage the epithelium, and therefore not only do the albumoses pass out, but some proteids of the blood-plasma pass out also. That is a typical example of albuminuria from blood-changes. The primary mischief is the alteration of the blood by the presence of large quantities of albumoses, and this affects the kidneys, with the result that there is an excretion both of the albumoses and also of the proteids of the blood-plasma.

The second variety is the albuminuria from passive congestion of the kidneys, as, for instance, in heart disease, and in tumours, &c., pressing on the vena cava. The albuminuria from partial thrombosis

of the renal veins is an extreme example of this form of albuminuria, as is also the albuminuria seen in mitral disease. The albuminuria seen in pregnancy is possibly dependent upon the action of a toxic substance on the kidney, and not simply upon the pressure of the uterine tumour on the renal veins. At one time it was usual to describe an albuminuria caused by high tension; but it is probable that this view is erroneous, and that the albuminuria seen in cases of high tension is really dependent upon an accompanying renal lesion.

The third variety of albuminuria is that arising from primary organic disease of the kidney or of some part of the urinary tract. To recapitulate the varieties I have described, there is, firstly, albuminuria from primary blood-changes, or toxic albuminuria; secondly, albuminuria from venous congestion; and thirdly, albuminuria from primary changes in the kidney or urinary tract. You may add albuminuria from rupture of an abscess or hæmorrhage into some portion of the urinary tract.

The amount of proteid matter that may be lost in the urine is often very considerable when you bear in mind that you may get nearly as much proteid matter per cent. in the urine as in the blood-plasma. There is about 8 per cent. of proteid in the blood-serum, and the urine rarely contains more than 6 per cent., so that there may be almost the same percentage amount of proteid matter in the urine as in the blood, and hence the loss may be very considerable. The maximum loss may be

something like forty or fifty grams daily ; and forty or fifty grams, to put it in more homely terms, is about as much proteid matter as there is in from two to two and a half pints of milk. A patient with certain forms of renal disease may lose from his kidneys very nearly as much proteid matter as there is in a full hospital diet of milk, hospital patients on milk diet taking about three pints of milk per diem. It is a very considerable amount to lose, and though you will sometimes see it stated in books that the amount of albumen lost by the kidneys is not of consequence, I am sure, to say the least of it, that that statement is not a correct way of expressing the fact. In the cases where the highest percentage of albumen occurs, where the urine boils solid, the amount of urine is usually small, and hence you do not get a very great loss, notwithstanding the fact that the urine when boiled is solid. When the urine is much increased there is often a greater total loss of albumen, although the percentage amount of albumen may be much less than when the urine boils solid. The maximum loss of proteid is most often seen in cases of waxy kidney, and more especially, perhaps, in a particular variety of chronic Bright's disease, where the quantity of urine is considerably above the normal, and where it contains a considerable percentage of proteid. The maximum loss of proteid is more often seen in these cases of chronic kidney disease than in cases of acute Bright's disease. The gravity of a case of Bright's

disease is not measured entirely by the amount of albumen that is lost; in many of the most serious cases of Bright's disease very little albumen may be lost, and it is possible for severe and fatal uræmia to occur without albuminuria.

The most important varieties of proteids met with in the urine are albumoses, globulins, and albumins. Nucleo-albumins are sometimes present in the urine, and sometimes true peptones are said to occur in the urine; but these are more or less curiosities, and are not of any great clinical importance. The proteids we are really concerned with are albumoses, globulins, and albumins. The first point is never to forget that you may have albumoses in the urine without any other proteid matter, and if these albumoses are present they may not be detected in the ordinary routine examination of the urine. Although albumoses may be present alone in the urine, it is more common for a mixture of proteids to be present. Albumosuria is, strictly speaking, the name given to the condition where albumoses only are present, but sometimes it is applied to cases where these bodies are present along with other proteids. In febrile states albumoses are found frequently in the urine, and in any disease that is associated with the presence of microbes, and more particularly in cases where the microbes present are those connected with suppuration. Empyema is a typical instance for demonstrating the presence of albumoses in the urine; and the same is true of

pneumonia, in which, although there is no suppuration, still there is a fibrinous exudation. In these and other similar cases the albumoses damage the kidney to a sufficient extent to allow a small amount of albumen to pass through, and you then have febrile albuminuria, or what the French call transitory nephritis.

Other febrile conditions besides those associated with empyema and pneumonia probably produce the albuminuria associated with them in this way. At the same time the excretion in febrile states of other toxic substances besides albumoses may lead to albuminuria. This form of albumosuria, with or without albuminuria, and associated with some febrile disorder, is mainly of scientific interest; but there is one form which is important, and that is the albumosuria that occasionally occurs in granular kidney, and perhaps in other forms of renal disease. There are occasional cases of granular kidney in which albumosuria is a marked feature, and the patient's urine may contain quite a large amount of albumoses, far more than is seen in what may be called febrile albumosuria. The only renal disease in which albumosuria is at all marked is this form of granular kidney; but I have seen albumosuria considerable in amount in two cases where the condition of the urine suggested the existence of chronic diffuse nephritis. Albumoses are not coagulated by heat, and if the urine is examined in the ordinary routine fashion their presence may

not be detected. It is difficult to understand the cause of this copious albumosuria in chronic renal disease, inasmuch as it occurs without there being any inflammatory complications to cause it. It has been suggested that it has an intestinal origin, and that owing to some disturbance of digestion and assimilation the albumoses formed in digestion are absorbed as such into the blood-stream, and subsequently excreted. This view is plausible, but there are no facts, as far as I know, to really substantiate it. Another condition in which considerable albumosuria may be present is in ovarian disease. There was a case here recently where the urine contained such an abundant quantity of albumoses as to become nearly solid when the albumoses were precipitated. The explanation of these cases is, as far as I know, unknown, inasmuch as the ovarian tumour was not a suppurating one.

In cases of so-called albuminuria the proteid matter present is usually a mixture of serum-albumin, serum-globulin, and traces of albumose. In many cases of albumosuria there is a certain amount of albuminuria, but the converse is not true. Some years ago an attempt was made to show that the presence of globulin had a different significance from the presence of albumen, but there is no ground for that belief. Peptonuria is said to exist, but many cases are really cases of albumosuria, and cases showing the presence of true peptone in the urine are rare; suckling women are said to

exhibit this. Besides confusing albumosuria with peptonuria, there is another possible fallacy; since the urine contains traces of pepsin, if the examination is delayed it is quite likely that peptone may be formed afterwards.

As regards the tests from a clinical point of view, many tests that are suitable in the laboratory are not suitable clinically. Picric acid is a test that is largely used for proteids, and it is a very delicate test, but it has this drawback, that for many clinical purposes it is too delicate; you will get a reaction in the cases of physiological or functional albuminuria, and you may be misled into thinking that it is a serious condition; therefore picric acid is most valuable when functional albuminuria is suspected. It is not a good test to examine urine straight away with. In the country you can carry it solid, which is perhaps a good point in its favour. As regards the ordinary tests, one relies on nitric acid, but different people will give you different advice. Personally I always teach that the nitric acid test on the whole is the best test, and at any rate it ought always to be used in the routine examination of the urine, since by its use albumoses may be detected as well as the ordinary proteids. It is not, however, a very delicate test, it does not compare in this respect with the picric acid test; but if the urine does not react to the nitric acid test, there cannot be any very serious condition, except some cases of granular kidney, where occa-

sionally only the merest trace of albumen is present, or even none. The nitric acid must not contain nitrous acid, otherwise the urine effervesces, and the essence of the test is that the urine and the acid must not mix. You must float your urine on the top of the acid, and not mix the urine with the nitric acid; if you mix it up the nitric acid may easily dissolve a small quantity of albumen. Another point is that you must leave it to stand for some minutes; if there is only a small quantity of albumen the ring does not come out strongly for some minutes. If you follow the rule of not using nitrous acid, and of floating the urine on the top of the nitric acid, you will have no reason to complain of the test.

The only fallacies are, if there is a small amount of albumen, you may dissolve it with the nitric acid. If you are very careless you may mistake nitrate of urea for a ring of proteids, but that would be a gross mistake to make. The administration of some resinous bodies, *e.g.* copaiba and turpentine, causes the excretion in the urine of a substance that may yield a cloudiness on the addition of nitric acid.

As regards the heat test, you can acidify the urine first, or you can acidify it afterwards. The usual thing to do is to acidify it first. When you acidify, you must be careful to acidify with a weak acid, such as acetic. It is well to boil urine in the usual clinical way, at the top first of all, so as to be able to compare any cloudiness with the lower

part of the tube, to see if the opacity increases. If you have a urine that is only very slightly acid or alkaline, and you boil it, the earthy phosphates are precipitated for reasons which we shall see later on; the precipitate in some way resembles a proteid. You clear the point up at once with a drop of acetic acid, but the earthy phosphate fallacy has only to be mentioned to be dismissed. If the urine is not acid enough, and there is only a small amount of albumen present you may have it converted into an alkali-albumen, and it will not then be precipitated. The test for albumoses is to take about half a test-tube of urine and drop nitric acid into it gradually. This precipitate of albumose will disappear on heating, but inasmuch as in many cases of albumosuria there are other proteids also present, when you warm it it may not entirely disappear, the cloudiness may only diminish, to increase again on cooling. That is a rough test for albumoses; and if with this test a result is obtained, the more delicate sulphate of copper and caustic potash test, which gives a violet colour with the proteid matter, and a rose colour with albumoses, may be used as a further confirmatory test. For accurate purposes the albumoses may be separated from other proteids by depending upon the fact that whereas ammonium sulphate precipitates all proteids except true peptones, magnesium sulphate precipitates globulins, and sodio-magnesium sulphate precipitates also albumins; so that by using these salts and washing the pre-

cipitates with saturated solutions of the corresponding salts, the albumoses, globulins, and albumins present in the urine may be differentiated. These, however, are methods more adapted to the laboratory, and are as yet of no great clinical importance.

If the urine contains a large quantity of proteid matter, on pouring it into distilled water a precipitate will be seen, and this is dependent on the precipitation of globulin. In an ordinary case of Bright's disease, if you pour the urine drop by drop into distilled water the globulin will be precipitated. In some cases ordinary water may be used where the amount of proteid present is very large. If you are without apparatus of any kind the urine may be acidified with vinegar, and boiled in a spoon over a candle.

As regards the estimation of the quantity of proteid present, the best way is to precipitate the proteid by adding 5 c.c. of the urine to some 50 c.c. of boiling absolute alcohol, and filter ; wash the precipitate with alcohol, ether, and water, and then after drying weigh the precipitate; all other methods are more or less inaccurate. It is not generally desirable to determine the amount actually, it is only of scientific interest. The clinical method of determining roughly the amount by the subsidence method is probably as good as any. The urine is boiled after acidification, and the relative bulk of the precipitate to the volume of the urine determined after allowing the urine to settle for twenty-four hours. The state in which

the precipitate is thrown down, whether it is a coarse or a fine precipitate, depends on the amount of salts and acids present, and they also influence the degree to which the coagulum contracts afterwards. Personally, I think the ordinary subsidence method is accurate enough for most purposes. Esbach's method is a modified subsidence method, and is said to be more accurate; it is a method of precipitating urine with citric acid and picric acid. My own experience of this method in this hospital has not impressed me with its accuracy, and very often the determinations as checked by the weighing method were 100 per cent. wrong, so that personally my advice is to be satisfied with the ordinary subsidence method, unless you wish actually to determine by weight the amount of proteid present.

Now as to the significance of albumen, that is to say, the prognosis of albuminuria. The significance of course varies from a trifling significance in some functional cases to a very grave one. What do you express your opinion upon? You do not express it solely on the percentage amount present: for instance, a pregnant woman may have her urine showing a third albumen, and clearing up completely at delivery, with no permanent ill effects; and some authorities hold that you may have the urine solid with albumen without any permanent structural disease of the kidneys. You may certainly have large quantities of albumen present in the urine, as in pregnancy,

without there being any condition which destroys the patient. On the other hand, in a patient with granular kidney you may have little or none, and yet the disease is rapidly fatal, therefore you must not express any opinion on the percentage amount of albumen. In these cases of pregnant women passing large quantities of albumen they pass a very small amount of urine. A patient with a granular kidney passes very considerable quantities of urine, and the amount of albumen is of course more than you would think, hence all considerations of percentage amounts of albumen must always be checked by considering the total quantity of urine. Although of course, broadly speaking, the greater the amount of albumen the greater the damage, this is not always true.

With regard to albumosuria, it is a trifling matter excepting in relation to the granular kidney of which I have spoken, which is always a very severe and grave malady, so the variety of proteid matter is of some but not of great importance. Febrile albuminuria does not leave any permanent lesion of the kidney. You base your opinion then most of all on the general condition of the patient, the state of the pulse, the presence or absence of dropsy, &c., on the microscopic examination of the urine, and on the nature of the formed elements you may find in the urine, and more particularly what casts you find. I would warn you at once that hyaline casts are not of any great consequence, they are probably nothing but coagulations of the

blood-plasma in the renal tubules, and are not of any grave significance; but epithelial and still more fatty casts are of grave significance, so also are waxy casts. The presence of pus and so on will often throw light on the matter, and I want to digress here for a moment. Supposing a urine to contain pus, you must always examine the supernatant portion of the urine, after allowing the deposit of pus to settle. You should syphon off the urine, not stir it up at all, and examine also the upper part. There was a certain patient with a large quantity of pus in the urine, stone was diagnosed, the urine was simply boiled, albumen was found, and there was pus. A nephrotomy was done, and no stone found, and the patient died almost immediately of uræmia; she had pyelitis and amyloid disease of the kidneys. If the supernatant portion of the urine had been examined more albumen would have been found in the urine than could have been accounted for by the pus, and thus the existence of renal disease might have been suspected, and therefore the operation contra-indicated. If you have a large quantity of pus in the urine there must be albumen in the urine from the pus, therefore you let the urine stand and pour off the supernatant fluid; but if you find a quarter or a third albumen in the supernatant fluid, it would be probable that the pus alone could not cause it. In the prognosis of albuminuria you must take into account the state of the circulatory system, the state of the pulse, and the presence or absence

of albuminuric retinitis. There is one other remark about the presence of albumen in the urine; the presence of large quantities of albumen interferes with the test for sugar, Trommer's or Fehling's test. If you have a large amount of albumen, a third, quarter, or a half, the sugar reaction does not come off; therefore in examining the urine for sugar, examine first for albumen. If you find a considerable quantity of albumen, precipitate it and filter it off, and then test for sugar. It does not apply to most cases of diabetes, because in diabetes, even if albumen is present, the quantity of sugar present is usually so large that the test is not interfered with; but sometimes it is otherwise, and the presence of sugar may be overlooked.

No. III.

We will consider to-day the question of the colour of the urine, that is to say, the pigments, normal and abnormal, that the urine may contain. The urine is described as being normally straw-coloured; the depth of colour, however, varies considerably. As regards the cause of the normal colour, we must consider mainly the points that are of clinical importance. It used to be taught that the urine owes its colour mainly to a single pigment, urobilin, but that in addition to this coloured body it was stated that the urine contains a colourless substance spoken of as a chromogen, which on the addition of an acid becomes converted into urobilin or a modified form of urobilin known as febrile or pathological urobilin. There is, however, no doubt that this view is not correct, since the pigment causing the normal yellow colour of the urine is not soluble in chloroform, and, on the other hand, urobilin is soluble in chloroform. The colour of the urine is therefore certainly not entirely due to urobilin, but the urine contains some urobilin. The yellow colouring matter to which the urine owes its colour is best called, as Thudichum called it, urochrome. This substance can be extracted by appropriate methods from the

urine, and it is found that it does not yield a banded spectrum; and the bulk of the colour is due to this yellow pigment, urochrome. In addition to urochrome there is a certain amount of urobilin, a pigment also found in the bile. Whereas urochrome is insoluble in chloroform and yields no spectrum, urobilin is soluble in chloroform and yields a definite spectrum. In the normal urine there is also a certain amount of uroerythrin, a substance which colours urates pink, and which is present in greatly increased amounts in various diseases. Another pigment present in the urine in small quantities in health is the iron-free derivative of hæmoglobin, hæmatoporphyrin. There are thus at least four pigments in the urine: urochrome, which is the most abundant, urobilin, which is present in small amounts, uroerythrin, in smaller amounts, and hæmatoporphyrin, in traces only. In addition to these pigments the urine contains a number of substances which are perhaps best described as chromogens, bodies which do not impart a colour to the urine, but which under the influence of oxidising agents become coloured. Some of these chromogens are bodies like indol and skatol and their allies, which are present, combined with sulphuric or glycuronic acid in the form of aromatic sulphates. Thus, indoxyl sulphate of potash and skatoxyl sulphate of potash are substances which are not themselves coloured, but which on the addition of mineral acid yield coloured bodies, and assist to form the ring of

colour which is seen on pouring urine on to nitric acid. One of the most interesting of the bodies coming under the classification of substances which are not pigments till they are oxidised, is the body indican (there are 20 mgrms. of this substance in the urine in the twenty-four hours), and this is readily converted into indigo by adding hydrochloric acid. The facts that one wants to impress are that, first of all, there are at least four pigments in the urine, and that besides these, there are other substances which are not pigments, but which become so on the addition of acids. A further point of interest, as regards the origin of the urinary pigments, lies in the fact that if owing to a biliary fistula a patient discharges the whole of the bile through the abdominal wall to the exterior, you will find the urine apparently quite normal in colour. Thus, if no bile enters the intestine, the urine still retains its typical straw colour ; that is a fact that has been known for several years, and it is a very serious objection to the view that the urinary pigments are formed from retrogressive changes in the bile pigments in the bowel. A patient I saw discharged the whole of his bile through a fistula, and at the end of a year his urine was still quite typical in colour. The question of the origin of the urinary pigments scarcely concerns us here, but the blood pigment of the body and of the food in addition to the bile pigments may be the sources from which these urinary pigments are ultimately derived.

Urobilin is readily separated from the urine, and sometimes it is of interest, I cannot say it is of great importance, to do so in certain diseases, pernicious anæmia for instance; all that is necessary is to take some urine and precipitate it with lead salts, the precipitate of lead salts carries down the pigment with it, and this is collected on a filter, and extracted with alcohol containing a few drops of sulphuric acid; in this way the urobilin is obtained in an alcoholic solution, and its spectrum can be readily determined, and this is a much more satisfactory method than that of examining the urine itself spectroscopically. The normal urine rarely yields more than a shading at the violet end of the spectrum; but if a large quantity of urobilin is present, the band typical of this substance may be seen without extracting the urine as described.

In regard to the colour of the urine it undergoes great changes in disease; thus it may be almost colourless, as in diabetes insipidus, greenish as in diabetes mellitus, brownish black as in melanuria, blue as in some cases of indicanuria, greenish brown in jaundice, red in hæmaturia, black in carboluria, &c. A satisfactory classification of the pigments present in disease is rather difficult of attainment, and I will, therefore, only divide them into two groups, the first consisting of the conditions where the abnormal colour of the urine is dependent upon the presence in excessive amount of some normal urinary pigment, and the second group where the abnormal colour is dependent on

the presence of an abnormal pigment. We will consider the group where the abnormal colour of the urine is due to the presence of a normal pigment in excessive amount first.

Urobilinuria.—Urobilin is present normally in small quantities, and does not appreciably colour the urine, the colour being due to urochrome. When there is much urobilin in the urine, it is usually brownish-red in colour, but it may be more brown than red, so that it is mistaken for bile, but on the other hand it may sometimes be sufficiently reddish that it is mistaken for blood. I must warn you at the very outset that urobilinuria is often not recognised, and many mistakes are made when there is a very large amount of urobilin present in the urine; competent observers may think from the naked-eye appearances that the urine contains blood or bile according as it is red or brownish. Patients who pass a large amount of urobilin in the urine are frequently yellow, that is to say, they are apparently jaundiced, and sometimes they are very yellow, but they are not really jaundiced if you use the word in its strict sense, and that sense is a person who is yellow from the presence of bile pigments in the tissues of the body, and this is not of course synonymous with a yellow person.

The cause of urobilinuria is usually simple, it is due to a decomposition of blood pigment, a breaking up of hæmoglobin in some part of the body, and this breaking up of hæmoglobin may occur inside the blood-vessels, as in the disease known as

paroxysmal hæmoglobinuria, or external to the blood-vessels as in other maladies.

Paroxysmal hæmoglobinuria is usually an affection of people who have lived in hot climates; its nature is not fully understood, but the red blood-corpuscles are more fragile than normal, and the red blood-corpuscles disintegrate, apparently within the vessels, and the hæmoglobin is liberated into the blood-stream and excreted in the urine in the form of hæmoglobin, methæmoglobin, and urobilin. Another instance of urobilinuria dependent upon increased blood destruction is afforded by pernicious anæmia; in a marked case of this disease the patient is lemon-tinted and the urine is dark, notwithstanding that the patient is extremely anæmic, whereas most patients with anæmia pass a urine light in colour, these patients with pernicious anæmia are yellow and pass a dark urine. Both the lemon tint of the patient and the dark colour of the urine are due to the presence of urobilin in excess. Another instance of a slighter degree of urobilinuria is seen in septicæmia; many patients with septicæmia or pyæmia are yellowish and pass urine dark from excess of urobilin. One of the most interesting and important forms of urobilinuria is where the condition arises as a result of a large internal hæmorrhage, which is very frequently abdominal. These cases of abdominal hæmorrhage are often due to causes which do not necessarily lead to death, whereas large hæmorrhages in other situations are perhaps more often

immediately fatal. A large hæmorrhage in the pleura, for instance, is usually due to rupture of an aneurysm, and the patient dies rapidly ; but not uncommonly you get large hæmorrhages into the peritoneum or retro-peritoneum without death occurring, at any rate, immediately, and it is very striking to watch these cases. A few days after the hæmorrhage the patient may become feverish and apparently jaundiced, and passes urine which is dark brown in colour, and often supposed to be bile-stained, whereas it is really urobilinuria. You will probably see such a case sooner or later, and it is a thing that when once seen you will have no difficulty in again recognising. A case in point is that of a man who was operated on for hernia and had some omentum removed ; some hours afterwards he became rather collapsed ; nothing was noticed till a few days later, when he got feverish and apparently jaundiced, and passed urine containing much urobilin. The reading of the case was that there was probably a slipping of a ligature and a large hæmorrhage. Another similar case is the following :—A woman who had not menstruated for several months had sudden pain in the abdomen, and became suddenly collapsed. It was supposed that she had an intra-abdominal hæmorrhage, such as a pelvic hæmatocele or ruptured tubal gestation ; the abdomen, however, was not opened. A few days afterwards she became apparently jaundiced ; she passed this dark urine containing a large quantity of urobilin,

and subsequently got well; and although the diagnosis was not confirmed, it is probable that some hæmorrhage occurred.

There is this same condition of urobilinuria to a slight extent in many diseases, and more particularly in febrile diseases; but diseases which are associated with disintegration of the red blood-corpuscles to a considerable extent, as those just mentioned, are the maladies in which marked urobilinuria is most apt to occur. I might give you a long list of diseases in which urobilinuria occurs, but it would not serve any practical purpose; nevertheless, I would mention especially purpura simplex and purpura hæmorrhagica, and here also the urobilinuria is dependent upon the disintegration of blood-pigment. Urobilinuria is readily recognised; the urine may look as if it contained bile, but the bile tests do not come off properly, and you may notice that on adding nitric acid, instead of the proper play of colours beginning with green (which is the important colour in the play when bile is present), there is an imperfect play of colours, but there is no green colour, and this should raise your suspicion as to whether bile is really present, and then you must use the spectroscope and seek for the presence of the urobilin band. Bile pigment does not give this band.

Hæmatoporphyrinuria.—There is a small amount of hæmatoporphyrin in the urine normally, but you will find large quantities under certain conditions. The administration of large doses of sulphonal to

patients will sometimes make them pass urine of a red colour. Hæmatoporphyrin imparts a very remarkable colour to the urine; it is not quite a cherry colour, it is more of a claret. This hæmatoporphyrinuria is seen especially after the administration of sulphonal, but it also occurs in disease, thus it is sometimes seen in rheumatic fever, in cardiac disease, and in Addison's disease. The causes and nature of it are obscure, but it has been supposed to be dependent on internal hæmorrhage, and especially on hæmorrhage into the alimentary canal. Hæmatoporphyrin can be extracted from the urine by the use of the method described above for the extraction of urobilin, and like urobilin it is identified by its spectroscopic characters.

Uroerythrin is increased in all febrile states, and is a pigment which is familiar to all as colouring urates pink.

The chromogens present in the normal urine are skatol and indol compounds and their allies in the form of aromatic sulphates. These bodies are formed in the intestines, and I will digress here to point out a curious function of the kidney. As every one is taught, the kidneys and the skin have a certain relationship, but the kidneys and the intestines have one also. It is very remarkable that these aromatic sulphates, which are more or less products of intestinal putrefaction, should not be excreted with the fæces, but that they should be absorbed from the intestines and excreted by the

kidneys. It draws your attention to the fact that substances are sometimes excreted by what, at any rate, seems a very roundabout channel. Some physicians have thought that uræmia may be really intestinal poisoning, since if the functions of the kidneys are interfered with, the patient may be poisoned from toxic bodies formed in his own intestine. These aromatic bodies tend to be excreted in the urine in far greater amount than normal when the putrefaction in the intestines is increased. In typhoid fever the intestines are swarming with the *Bacillus coli-communis*, and there is, at any rate, considerable decomposition of proteid matter; and such patients pass dense, high-coloured, brownish-red urines, which are loaded with these skatol and indol pigments. Another instance of the same thing is where there is increased intestinal putrefaction owing to intestinal obstruction; and even people who suffer from constipation only have yellow conjunctivæ, and pass dense, high-coloured urine.

In cases of intestinal obstruction there is an abundant excretion of these skatol and indol compounds, and this is especially the case in chronic obstruction, where the colon may dilate to a great size, and be full of liquid fæces undergoing decomposition, and hence it is easy to understand that the absorption of these pigments is considerable. Peritonitis is an instructive example of the same thing, and in this disease you get these substances in the urine, since, owing to the para-

lysis of the bowel, there is a considerable amount of putrefaction of the intestinal contents. These skatol and indol compounds are also present in the urine in increased amount when there is extensive suppuration in some parts of the body, as in empyema. Indican is a body of this type, inasmuch as indican is indoxyl potassic sulphate, and the term indicanuria is given to the condition where indican in excessive amount is excreted in the urine. Indican is formed in the alimentary canal from indol, and this is united with sulphuric and glycuronic acids as an aromatic compound, and is excreted by the kidney. In conditions where the intestinal putrefaction is increased, indicanuria is apt to ensue. Patients with intestinal obstruction may actually pass a urine which although not blue at the time of passing, becomes blue from the oxidation of indican to indigo, so that indicanuria has the same clinical significance as the presence of excessive amounts of skatol pigments in the urine. It points to the increased breaking down of proteid matter, and, although usually intestinal in origin, yet indicanuria may result from absorption from large purulent collections in various parts of the body. It is, however, more common as a result of intestinal obstruction and putrefaction, and one of the best instances is cancer of the rectum, since this disease runs a chronic course, and therefore you have every opportunity for increased excretion and absorption. The presence of large quantities of indigo in the urine

is easily detected; you take the urine and add to it about a quarter to a third of its volume of hydrochloric acid, and some calcium hypochlorite, let it stand for twenty-four hours, and then the blue scum is observed on the surface. Indigo is sometimes present in such a large amount as to form a calculus, and there is a celebrated specimen in St. Thomas's Hospital Museum.

There is a rare pigment occasionally present in the urine called melanin, and to this condition the name melanuria is given. It is a condition of some interest, but not of any great practical moment. These patients pass a urine which is the colour of *café au lait;* it is often muddy-looking, and when you proceed to test this with nitric acid it goes absolutely black, as you see in this specimen that I obtained some years ago. This is very characteristic of melanuria; it is extremely rare, and I have only seen this one case. The patient had had the eyeball removed for melanotic sarcoma, and came under observation some years afterwards with a number of large tumours in the liver, probably melanotic sarcomata. Melanuria is sometimes seen where you cannot recognise any cause, and it may be the only departure from health; but more usually it is seen in patients with melanotic sarcoma, but you must please understand that it by no means occurs always in melanotic sarcoma. Melanotic sarcoma is not a very rare disease, but melanuria is more rare than melanotic sarcoma. I only mention it for the sake of completeness.

The presence of *blood* in the urine of course alters the colour very considerably. First of all you must make the distinction between blood-corpuscles in the urine and blood-pigment without corpuscles; the former is usually spoken of as blood in the urine, and the latter as hæmoglobinuria, though as a matter of fact the pigment is in both cases hæmoglobin. Blood-corpuscles are found in the urine in a great number of conditions which are very roughly classified as follows:—Blood in the urine as the result of acute congestion of some part of the urinary tract, as the result of passive congestion, as the result of ulceration, and as the result of rupture into the urinary tract. For instance, you may have hæmaturia from the acute congestion of the kidney that results from acute nephritis, or from acute cystitis, or acute urethritis; these are all instances of blood in the urine from acute congestion. As regards passive congestion it is well known that blood may appear in the urine as the result of passive congestion of the kidneys, as in cardiac diseases, or, as in some cases of engorged prostate, where there is a long-continued distension of the veins of the prostate. Blood also results from ulceration, as in tuberculous pyelitis or in tuberculous and malignant disease of the bladder. Another cause is from rupture; this is rare, but it is conceivable, and recently I saw a case where hæmaturia apparently resulted from an aneurysm of the renal artery projecting into the renal pelvis, but this cause is un-

likely. Now as regards the amount of blood, there may be only a few blood-corpuscles or there may be so much blood that the blood coagulates in the bladder in one solid clot; as extreme instances one may mention a tuberculous kidney, from which you may have a very small amount of blood, or a villous tumour of the bladder, where the amount is often very large. A stone in the kidney may cause very scanty hæmorrhage or it may be profuse, and occasionally in tuberculous kidney there is very profuse hæmorrhage. A more important question than the amount of the blood is the source of the blood, and you remember the fundamental point, that if the blood is of renal origin (and it is convenient to include the hæmorrhage from the renal pelvis under the heading of renal hæmorrhage), the blood is intimately and uniformly mixed with the urine. On the other hand, if the blood come from some other part of the urinary tract, it probably is not so intimately mixed with the urine, but it may be. Thus in hæmorrhage from the bladder the blood is not necessarily mixed with the urine, though it may be, and the usual typical bladder hæmorrhage is characterised by the fact that the first portions of the urine are clear, and the latter portions blood-stained; that is the typical condition in cases of hæmorrhage from the bladder, including the prostate, but it is a rule liable to many exceptions. As the bladder contracts down on the diseased structure or surface, the hæmorrhage is produced,

and therefore the urine voided during the latter part of the micturition contains more blood, and it is a very characteristic thing of prostate hæmorrhage that the very last portions are full of blood. Occasionally in prostatic and urethral hæmorrhages, the first portions of the urine contain most blood; it is a thing that one reads about but does not often see. To consider more in detail some of the causes of blood in the urine: in acute nephritis you have hæmorrhage from the kidney; as a rule the hæmorrhage is not very abundant, because you must bear in mind that in acute nephritis the quantity of urine passed is small, so that the hæmorrhage as a rule is not very profuse. The hæmorrhage accompanying infarction of the kidney is also usually scanty. In pyelitis, the acute congestion of the pelvis of the kidney results from the inflammation of the pelvis, accompanying the presence of stone or tubercle. In passive congestion, as, for instance, in heart disease, the blood is usually small in amount, the urine is often only just tinted.

The hæmorrhage that occurs occasionally in the granular kidney is a difficult form of hæmorrhage to classify. These patients are liable to various hæmorrhages; they readily bleed from the nose, and every now and then they bleed copiously from the urinary tract, and the amount of blood lost is often large. Many of these patients are fairly well, they have not complained much, and they may come to the medical man for the profuse hæmorrhage, and

it may be thought that they have malignant disease of the kidney, but they really have a granular kidney. These very profuse hæmorrhages in cases of granular kidney are probably hæmorrhages from the mucous membrane of the renal pelvis, and not from the true kidney substance. Another disease which produces very copious and alarming hæmorrhage, of which the mechanism is not well understood, is purpura hæmorrhagica, where you get very severe bleeding, and it is known that this hæmorrhage is from the pelvis of the kidney, since on post-mortem examination a remarkable condition is found. On slitting up the kidney and the ureters the kidney substance is found healthy, but the whole mucous membrane of the ureters and renal pelvis is raised up from the presence of blood-clot underneath. The hæmorrhage undoubtedly occurs from the pelvis. It is frequently not recognised that the source of the bleeding is the renal pelvis and not the kidney substance, and you must bear in mind that you may have a dangerous and even a fatal hæmorrhage from the pelvis of the kidney in cases of purpura hæmorrhagica. Hæmorrhage from ulceration is seen especially in calculous and tuberculous pyelitis, and in malignant disease of the kidney.

There are two diagnostic problems connected with hæmaturia, one to diagnose the presence of blood in the urine, and the other to determine its source. There is nothing to equal the microscope in determining the first point, every other test is a long way behind it, there is no test for blood so

delicate as seeing the blood-corpuscles. One may not be always familiar with the appearance of the blood-corpuscles as seen in the urine, their colour is not very striking, you may easily think it is a pus-cell; and in the second place it may be profoundly altered, if it is a dense urine it is crenated, and may then be mistaken for a pus-cell; on the other hand, if it is a dilute urine it may be swollen out so as to be almost bursting. As regards the other tests, speaking with all due deference to the spectroscope, it is, on the whole, of very little use, except in the case of a man who has spent a great deal of time with it, which the ordinary medical practitioner has not done. It is a very good thing to use if you are familiar with it, but otherwise it is not an instrument to use for the recognition of blood in the urine in the form of blood-corpuscles. If you use a spectroscope the point is this: you do not rely on the presence of the two oxyhæmoglobin bands, but the point you rely on is the replacing the two bands by a single band on reduction; you must combine the chemical with the physiological condition. There are many substances that yield bands resembling the oxyhæmoglobin bands. The guaiacum test is a very good one, though the chemists sneer at it. A large number of bodies yield the guaiacum test, but they are not bodies which are usually found in the urine, and consequently it is not a bad test; the only point about it is, if you want to do it properly you should put your tincture of guaiacum

in the urine, shake up the two and then pour the ozonic ether on the top, so as to get a good line of demarcation between the two. Iodide of potassium will give a reaction something like that yielded by blood, with the guaiacum test, but the colour is more green and diffuse, and the blood one is more blue. The hæmin crystals test is a very good test. These are the principal methods by means of which you detect the presence of blood. There are none of them so good as the microscopical test.

IV.

GENTLEMEN,—Last time we considered the question of the recognition of blood in the urine, and there now remains the question as to how you determine what part of the urinary tract the blood has come from. Hæmorrhage from the kidney substance, as in acute Bright's, gives blood-casts, that is what tells us absolutely that the hæmorrhage is derived from the kidney substance. Blood-casts are to be seen not only in active, but also in passive congestion, as in cases of mitral disease, so that the presence of blood-casts gives no information as to whether the hæmorrhage is from active or passive congestion, but it only gives evidence that the hæmorrhage comes from the kidney substance. In some cases of granular kidney copious hæmorrhage occurs, and it is probably derived from the pelvis of the kidney, and under these circumstances blood-casts are absent, but a considerable number of the pyriform epithelial cells characteristic of the renal pelvis and of the ureter may be found, and in this way the diagnosis that the hæmorrhage comes from the pelvis may be made. Another instance of the same thing is in purpura, where profuse renal hæmorrhage, not from the

renal substance, but from the renal pelvis, may occur, and blood-casts are often conspicuous by their absence. In diseases of the bladder you rely mainly on the absence of casts, and on the fact that the blood and the urine are not uniformly mixed; and there may be other evidence, such as the presence of fragments of villous growths, as these form one of the common causes of profuse hæmorrhage from the bladder, so that the diagnosis of the seat of the hæmorrhage in cases of hæmaturia is mainly determined by the presence or absence of blood-casts, pelvic cells, renal cells, fragments of growth, and so forth.

The presence of blood-pigment in the urine, apart from blood-corpuscles, must now be considered. You have blood-pigment in the urine without blood-corpuscles in all cases in which the blood-corpuscles are disintegrated inside the blood-vessels. You will remember that in cases of urobilinuria there is an excess of urobilin in the urine, a result of the disintegration of blood-corpuscles; but urobilinuria occurs more especially if the disintegration occurs outside the blood-vessels. If the disintegration of the blood-corpuscles takes place inside the blood-vessels with the liberation of hæmoglobin in the blood-plasma, blood-pigments appear in the urine. The pigments are principally hæmoglobin and methæmoglobin, more often the latter than the former; acid hæmatin and hæmatoporphyrin may also occur, but the pigments we are really mainly concerned

with are hæmoglobin and methæmoglobin. If you disintegrate the blood-corpuscle in the vessels experimentally by the introduction of water into the circulation, or by the injection of glycerine, you get this hæmoglobinuria, and under these circumstances you get much more hæmoglobin than methæmoglobin, so that the urine is red. In disease methæmoglobin is the more common, and hence the urine is of a brownish-red or chocolate colour, and sometimes it is absolutely porter-coloured, owing to the large quantity of methæmoglobin and acid hæmatin present.

The main point is that when you break up the blood-corpuscles you have hæmoglobin itself in the plasma, and under these circumstances a portion of it is always excreted as methæmoglobin. After the experimental injection of water into the circulation you always have a certain but relatively small amount of methæmoglobin excreted in the urine. It is not definitely known where the transformation of hæmoglobin into methæmoglobin occurs; but it is certainly not in the urinary bladder, because the methæmoglobin can be detected in the urine obtained by catheterising the ureters, therefore it is either in the kidney or in the circulation; thus if hæmoglobin alone is extravasated into the blood-plasma the hæmoglobinuria is always associated with methæmoglobin, and this causes the brownish colour of the urine. This excretion of hæmoglobin and methæmoglobin is seen as the result of the action of certain poisons.

One that produces it to a great extent is arseniuretted hydrogen. Several people have lost their lives in preparing arseniuretted hydrogen. At the opposite end of the scale you have a substance like chlorate of potash, which in large doses is said, in children (I do not know if it has been observed in adults), to do the same thing, *i. e.* to disintegrate the blood and cause the excretion of methæmoglobin in the urine.

There is one substance — glycerine — which should be noticed, because it is perhaps of importance in this relation. If glycerine is injected into the circulation, this porter-coloured urine will be the result. In the human subject, of course, we do not inject glycerine, but glycerine is largely used for the purpose of acting as an enema, and of recent years there has been a use of it to induce labour and also to procure abortion. The point about it is that, if injected into the circulation, it infallibly produces this hæmoglobinuria. I mention this to you because a case has lately occurred where a patient had hæmoglobinuria after abortion had been procured, and died from the results of the hæmoglobinuria. We do not know that glycerine had been used, but it is possible. If large quantities of glycerine were used for this purpose, and if some of it were absorbed, it is possible that it might have caused the hæmoglobinuria. Hæmoglobinuria when severe may cause complete suppression of urine. There are a number of other substances which, like pyrogallic acid, toluene

diamine, pyridin, aniline, &c., will cause this condition, but they are not very likely to be taken. Snake poison will also cause this disintegration of the blood-corpuscles, and so lead to methæmoglobinuria. There are a number of toxins in disease which will also cause it, and it is undoubtedly the fact, though it is uncommon, that it may occur in septicæmia. The common conditions (putting aside the chemical poisons, snake poison, and the toxins from various acute diseases) that cause hæmoglobinuria are two diseases, paroxysmal hæmoglobinuria and Raynaud's disease. They are neither of them very common diseases, but you will probably see cases of both of them. In paroxysmal hæmoglobinuria—you have already heard that it is one of the causes of urobilinuria—the blood-corpuscles break down with extraordinary ease. A man in this hospital suffering from this disease in the course of three days lost more than half his blood-corpuscles. This disintegration of blood-corpuscles inside the vessels occurs with great suddenness; a man may be fairly well, and yet on getting up and going out for a walk on a cold day the attack will suddenly come on, and very large quantities of blood-pigment will be passed in the urine. You understand that all that happens in these cases is that the corpuscles break up inside the blood-vessels and liberate the hæmoglobin which is excreted by the kidney in the form of hæmoglobin, methæmoglobin, and urobilin, producing the well-known porter-coloured

urine. You sometimes see a similar thing in Raynaud's disease, which is a local asphyxia of the fingers, toes, and ears.

These are the principal conditions under which you get hæmoglobin and methæmoglobin in the urine. Some observers say that it may occur in man as the result of taking quinine. I have no personal knowledge of this, but it is asserted that large doses of quinine will cause it. As regards the recognition of methæmoglobinuria, you can generally form a very shrewd suspicion, simply by the porter colour or reddish-brown colour of the urine, according to the relative proportion of hæmoglobin or methæmoglobin; but the only accurate method is, of course, the use of the spectroscope. With the microscope you do not see any blood-corpuscles, you sometimes see a granular detritus, probably the remains of blood-corpuscles, but you do not see individual corpuscles. It is also difficult to see the decolourised blood-corpuscles in the blood, and this raises the suspicion that perhaps the disintegration of the blood corpuscles does not occur within the vessels, although the stromata of the blood-corpuscles circulating in the blood stream have been described. In the urine you generally find a granular detritus, and a good many granular and hyaline casts. You must remember that this hæmoglobinuria damages the kidney very considerably, and that you may as the result of hæmoglobinuria get suppression of urine and death. It is uncommon

in paroxysmal hæmoglobinuria, but it is not uncommon in the toxic hæmoglobinurias. It has been described in diphtheria. So that the excretion of the hæmoglobin and methæmoglobin by the urine is not altogether an innocuous process; it damages the kidney as shown by the presence of abundance of casts under the microscope, and may lead to the suppression of urine and death. You recognise these pigments by the spectroscope. The oxyhæmoglobin is recognised by its particular bands, and the methæmoglobin is recognised by its bands, this latter having two bands somewhat like oxyhæmoglobin bands, but it has a third narrow band on the red side of the D line. Hæmoglobinuria is not a condition of great clinical importance, but it is of considerable interest because of the great quantities of hæmoglobin excreted without any blood-corpuscles. I need not say much about the presence of acid hæmatin in the urine. The hæmoglobin in the presence of the acid phosphate of soda in the urine, becomes converted into acid hæmatin, and acid hæmatin is perhaps responsible for imparting the dark brown colour to some cases of paroxysmal hæmoglobinuria and of hæmaturia. Hæmatoporphyrinuria is also mainly of scientific interest, and is especially seen in some cases after the administration of sulphonal.

Now we will pass on to the consideration of the presence of bile pigments in the urine. You will remember, as regards the bile pigments,

that inasmuch as the bile contains not only bilirubin but also urobilin, the discoloration of the urine in cases of jaundice is often due to a mixture of these pigments. In true jaundice there is not only bilirubin or biliverdin and their derivatives in the urine, but there may also be a considerable excess of urobilin. Bile pigments appear in the urine as soon as there is any material obstruction in the bile-ducts. The bile is normally secreted under a very low pressure indeed, and the presence of jaundice and of bile in the urine was considered difficult to explain, because the biliary pressure is so low that it was thought that the secretion would cease before the pressure in the ducts was sufficient to cause the bile to pass back into the tissues. In obstruction of the bile-ducts, however, the bile gets into the circulation through the lymphatics, and it gets into the blood-stream, not through the hepatic veins to any appreciable extent, but through the thoracic duct. As soon as the bile gets into the circulation it is excreted by the kidney. The kidney picks out the bile pigments and excretes them in the same way that peptones are excreted. Not only is that the case, but the kidney is, so to speak, such a delicate organ, with such a selective affinity for bile pigments, that you may have the presence of bile in the urine when the patient is not obviously jaundiced. This, however, is most apt to occur at the commencement of an attack of jaundice. Bile appears in the urine in cases of obstructive

jaundice very frequently previously to the discoloration of the skin.

On the other hand, cases are sometimes seen where, after long-continued obstruction, the skin remains yellow, but the urine is not discoloured. It is customary still to describe two varieties of jaundice, obstructive and non-obstructive, and I am afraid I must repeat what I said before, but it is very important to have clear ideas. The word jaundice is used in two senses: it is used by some people as simply meaning a yellow patient with yellow conjunctivæ, apart from what is making him yellow; it is used by others for a patient who is yellow from the presence of bile pigments in the blood. There is very little doubt that you never get true jaundice,—that is to say, a patient yellow from the presence of bile-pigments, unless the bile ducts are obstructed, so that there is no non-obstructive jaundice. The cases of so-called non-obstructive jaundice, *i. e.* yellow patients with yellow conjunctivæ, and in which post-mortem the bile-ducts are patent, admit of several explanations. In the first place, a considerable number of these patients are jaundiced because the obstruction is in the capillary ducts. Phosphorus poisoning, which is not seen so very frequently as it was ten years ago, is an instance of this. Phosphorus poisoning is a condition in which the patient becomes intensely jaundiced, and in which post mortem the bile-ducts are apparently patent, and this used to be quoted as an instance of

non-obstructive jaundice; the capillary ducts are blocked owing to a catarrh of the fine ducts, and the pouring out of a quantity of sticky mucus; although the large ducts are patent and not distended, the patient is really suffering from obstructive jaundice. That explains one great group of cases of non-obstructive jaundice. The others are not really cases of true jaundice at all, they are cases of urobilinuria, and, as we saw last time, the colour of the urine and the colour of the patient suffering from urobilinuria is somewhat similar to the colour of the patient suffering from true jaundice, so that the unequivocal sign of bile pigment in the urine means that there is obstruction in the bile-ducts, but it does not mean that you will see the obstruction in the post-mortem room, it may lie in the capillary ducts. It is very doubtful whether bile pigment is ever formed simply as a result of decomposition of extravasated hæmoglobin; and I think most, if not all cases of so-called non-obstructive jaundice admit of the explanation just given. Bile also contains bile salts, and it is a remarkable fact that in cases of complete jaundice you do not get any appreciable quantity of bile salts in the urine. It is difficult to detect bile salts in the urine in anything but traces; there are traces present, but you cannot detect them by examining the crude urine, you must use special methods, whereas bile pigments are detected with ease. You are all familiar with the tests for bile pigments; the best test is

to add fuming nitric acid to the urine in a dish, not in a test-tube. The characteristic reaction is not so much the play of colours as the fact that the play of colours commences with a green colour. Skatol and indol compounds may give a play of colour with oxidising agents, but they do not give the well-known green colour dependent on the formation of biliverdin, therefore if you do the test, do it on a plate, and lay stress on the initial green; you will not go far wrong if you do that. You may use the iodine test if you like, the shaking up the urine with a solution of iodine giving you a green colour, it is the same thing, an oxidising agent producing biliverdin. These tests are so good, and liable to so few fallacies, that it is not worth while going to the other tests, but a useful test is the sulphur test, *i. e.* the sinking of a fragment of sulphur in a fluid containing bile. If you want to determine the presence of bile salts, which you really never do want to do clinically, you must evaporate the urine and extract with alcohol, and you must examine the alcoholic extracts for bile salts with Pettenkofer's reaction. This test will not succeed in the majority of cases if the ordinary urine is used, owing to the fact that it contains such a small quantity of the bile salts. Dr. Brunton pointed out that if you have a case of intense jaundice you can get Pettenkofer's reaction by shaking the urine violently, and the characteristic colour will be seen in the froth. As regards the colour of the urine, that which contains bile is

always greenish at the top. It may be almost any colour in the substance of the urine; it may be red, brown, or it may be almost black. It depends entirely on the amount of bile present, but it is always greenish on the top, and none of the skatol, indol, and urobilin pigments cause the urine to be green on the top. There are clinically three varieties of jaundice: there is first of all the well-known class of jaundice which our patients call the "yellow" jaundice; then there is green jaundice, and finally there is black jaundice, which is a rarer condition. The question as to the colour of the jaundiced patient is largely a question of the duration of the obstruction. If this lasts for several months the patient becomes green, and a green tinge is often seen after as short a period as six weeks or two months; after about a year the patient becomes very dark. The green colour is obviously due to the pigment becoming converted into biliverdin, but in black jaundice the nature of the pigment is not so definitely known. There was a case in this hospital some years ago so black from jaundice that the man was almost indistinguishable from one of the darker races. That patient was suffering from cancer of the pancreas with complete obstruction of the bile-ducts, and the jaundice had lasted for more than a year. On the other hand, I have seen a patient jaundiced continuously for six years, but the colour of the skin never went beyond the green stage.

V.

GENTLEMEN,—We will consider to-day the nitrogenous constituents of the urine. The only nitrogenous constituents of the urine which are of clinical importance are urea, uric acid, and creatinin; the other nitrogenous constituents of the urine, although numerous, are of no great clinical importance. Creatinin, although present in much greater abundance than uric acid—there is nearly twice as much creatinin as uric acid—and therefore coming next to urea in amount, is of but little importance on account of its solubility. Uric acid derives its importance mainly on account of its insolubility. Creatinin reduces sulphate of copper when boiled in the presence of caustic potash, and so produces a spurious copper reaction. You do not get the bright red deposit that is seen with dextrose, but it sufficiently resembles this for it to be occasionally mistaken for sugar. Creatinin is present in considerable quantities in all wasting diseases; normally, there is about a gramme present in the twenty-four hours' urine, there being only about half a gramme of uric acid. A gramme, rarely as much as two grammes, is approximately the daily excretion of creatinin. It

is mainly derived from the creatin of the food; it is very doubtful whether any is derived from the creatin in the body, but it is undoubtedly derived from the creatin of the food. In wasting diseases the increased excretion of creatinin is probably derived from the creatin of the muscles, and in diseases such as cancer you may have a large quantity of creatinin in the urine. So that the main importance of creatinin lies in the fact that it is a substance producing a spurious copper reaction.

Uric acid is excreted to the extent of about half a gramme in the twenty-four hours in health; in disease there are larger quantities than that, sometimes as much as three or four grammes in the twenty-four hours. Uric acid in healthy conditions is not excreted in the urine as uric acid, it is excreted as a urate, and it exists in the blood also as a urate. You will remember that uric acid is a bibasic acid, and to save one the trouble of repeating its long formula we can represent it in a loose sort of way as H_2U, instead of the long formula which it has. Each molecule of uric acid has two atoms of hydrogen that are replaceable, and the urates represented by the formula M_2U, where M is a monobasic element, do not exist physiologically or pathologically, you can only make that urate of soda by laboratory methods. The biurate, which can be represented by the formula MHU, exists largely pathologically, and another name for it is the acid urate, and a familiar example of this salt is the acid urate of soda, which

forms the long needle-shaped crystals seen in gouty concretions. Uric acid is like oxalic acid in the fact that it has these two series of salts, and in addition there are also the quadriurates, which are represented by the formula MHU,H_2U. This is not simply a mixture of the first two series, it is a definite compound, which is called the quadriurate because there are four replaceable atoms, three of hydrogen and one of the base.

We need not consider here the alkaline urates of the formula M_2U, as they do not exist in physiological or pathological conditions, and the compounds to be considered here are uric acid, the acid urates, and the quadriurates. One of the most important properties of these bodies is their solubility: uric acid is soluble in about one in 14,000 of cold water; the acid urates are twice as soluble as that, and the quadriurates are freely soluble. Uric acid is thus almost insoluble, the acid urates are more soluble, and the quadriurates are very soluble. Under physiological conditions uric acid exists in the form of a quadriurate; normally uric acid is present in the blood and in the urine, always in the form of a quadriurate, and the pathology of gout on the one hand and gravel on the other is largely connected with the question of the conversion of the soluble quadriurates into the relatively insoluble biurates or uric acid. A familiar example of quadriurates is the uratic deposit that is found in febrile urine; that is practically pure quadriurates with various

bases, but more particularly sodium. If you want to get quadriurates in large quantities you must take the chalky urine of serpents, which also contains quadriurates. It is an extremely unstable substance; it is decomposed more particularly by water into uric acid and an acid urate, that is an important fact about it. It is decomposed by water in a very simple way, easily understood if you represent it by the formula MHU,H_2U. You cannot extract quadriurates from the urine by means of water; if you want to observe the properties of quadriurates you must collect the deposit of urates from a febrile urine, place some of the deposit on a filter-paper, wash it with alcohol to get rid of the urine, and in this way you can get more or less pure quadriurates. Then if some of the deposit is placed on a cover-slip, and some distilled water added, you can see the crystals of uric acid forming. One of the most important reactions of the quadriurate is this fact that water decomposes it into the acid urate and uric acid. When you consider the relative solubility, the action of the water is to convert a soluble into an extremely insoluble substance, that is what happens if you decompose quadriurates by the action of water. You can imitate the composition of the serum as regards salts by making up a solution containing $\frac{1}{2}$ per cent. chloride of sodium, and ·2 per cent. of sodium carbonate; this mixture dissolves uric acid freely, comparatively speaking; ·5 per cent. of sodium chloride and ·2 per cent.

bicarbonate of soda will dissolve uric acid freely in the form of a quadriurate. The interesting point is that supposing you make a solution like that, and keep it for twenty-four hours, it decomposes into the biurate, so that if you have a quadriurate in the presence of a liquid containing bicarbonate of soda, when it decomposes it does not split up into a molecule of the biurate and a molecule of uric acid, but it splits up into two molecules of the biurate. Water splits up quadriurates into uric acid and an acid urate, and this chemical action lies at the root of the pathology of gravel. On the other hand, the splitting up of a quadriurate into two molecules of biurate of soda is at the root of the pathology of gout. In gout the deposits are not of uric acid, but they are the deposits of biurate of soda; in gravel the deposit is uric acid: the two compounds are formed differently from the quadriurates.

The fact of the urine depositing a quantity of uric acid does not necessarily mean that the uric acid is in excess. We see that the daily amount of uric acid is about half a gramme. You pass sixty times as much urea. The source of the uric acid is more or less unknown; there are a large number of theories, but practically the source of uric acid in the healthy urine is by no means certain. The modern view is that it is derived from the disintegration of proteids containing nuclein, from nucleo-proteids, and that view is based on a large number of physiological facts,

and that at the present time is the theory which holds the field. Previously it was supposed that the uric acid excreted was dependent on deficient oxidation,—in other words, that we did not take in enough oxygen to oxidise all the proteid into urea. It has also been supposed to be associated with a particular kind of diet, but in health it is not due to any particular diet. Certain of the carnivora pass little or no uric acid; on the other hand, insects which are not carnivorous pass large quantities of uric acid. You cannot say that in health uric acid depends on diet; it is another matter in disease. You cannot order a diet which will in health lead to no uric acid at all being excreted; it is apparently due to a peculiar metabolism of the nucleo-proteids present in the food and in the body. Even on a diet of pure egg-albumen there is a certain amount of uric acid excreted. Therefore it cannot be looked upon simply as a matter of diet; diet of course has an influence upon it, and it has been shown that about three hours after a meal the amount of uric acid excreted increases enormously. At the first sight that might seem to imply that the excretion of uric acid was due to diet; but if you take a meat diet or a mixed diet, or one of white of egg, you still have this great increase in the uric acid excreted about the third or the fourth hour after the meal, and therefore it has been supposed that the uric acid is derived from the immense number of leucocytes which are used up in the process of

absorption. There is an enormous increase in the activity of leucocytes during digestion, and to this cause the excess of uric acid excreted has been put down. The important point is that uric acid is excreted in greatest percentage amount some three hours after a meal, and in a healthy condition it does not make any very great difference in the amount whether you have a simple diet, a mixed diet, or a diet of white of egg. Although this is the time when the largest quantity of uric acid is passed, this does not mean that this is the time when there is the greatest risk of uric acid being deposited in the urine. The deposition of uric acid in the urine is most apt to occur in the morning in the starving state before breakfast. I am talking of health, and not of disease; that is the time in the twenty-four hours that the urine is most likely to deposit uric acid; it does not contain more uric acid then, it contains less percentage than at any other time, but the urine passed before breakfast is usually an acid urine. After meals, especially if a large quantity of vegetable matter has been taken, an increased amount of alkaline salts is excreted; and hence, though the amount of uric acid is increased, the salts are increased also, and the uric acid is thus kept in solution as a quadriurate. A starving urine is poor in salts, although the amount of uric acid is comparatively speaking low; that is the period in which the spontaneous deposition in the urine is most likely to occur, and that will illustrate very

well that the deposition of the uric acid is not a thing dependent entirely on the quantity present. Febrile urines contain a very large quantity of urates, but it is quite a rare thing to see uric acid in such urines.

Now, in disease you must please keep these two problems separate: firstly, the amount of uric acid in urine; and secondly, the precipitation of uric acid as such. Urates are increased in all febrile conditions, for every one knows that one of the first and most obvious effects of fever is to cause copious deposits of these urates. The next most important point is that the amount of uric acid in the urine is very greatly increased in certain diseases of the blood, more particularly in pernicious anæmia, and in the disease known as leucocythæmia. You may have in these diseases as much as six grammes excreted in the twenty-four hours; these patients take very little food, and you can understand that this great excretion is somewhat remarkable, and to a certain extent it is a confirmation of the view that the uric acid is derived from nucleo-albumins, because the blood-corpuscles consist largely of nucleo-albumins. It has been taught that diseases of the spleen have an influence on the amount of uric acid. In gout the excretion of uric acid is increased after the paroxysm, and during the paroxysm there is an increased amount of uric acid in the blood, but nobody has ever yet conclusively shown that there is an increased production of uric acid. It has

been shown that there is an increase in the blood, and after the paroxysm there is an increased amount in the urine, but it has not been shown that there is an increased production ; it is possible that there is a want of elimination, hence the paroxysm. There is a negative point which is of some interest : in diabetes mellitus the nitrogenous metabolism is increased from the patient eating large quantities of meat, and the uric acid in the case of diabetics is not usually increased ; in gouty diabetes it is increased, but in a great number of cases of diabetes the uric acid is not increased. Garrod showed that the blood of the gouty contains an excess of uric acid, as he obtained crystals of uric acid by soaking a thread in serum acidified with acetic acid. That is a thoroughly established fact. Sir W. Roberts's observations show that when uric acid increases in the blood the alkalinity of this fluid accounts for the formation and precipitation of the acid urate of soda, and what happens in the gouty patient is that the uric acid slowly accumulates in the blood, then it suddenly becomes precipitated in the form of these needle-shaped crystals, and wherever these may be formed they may set up a great deal of irritation. Certain fluids of the body, more particularly synovial fluid, but other fluids also, cause the formation of acid urate of soda more rapidly than blood does.

To return to the urine, the main importance of uric acid in the urine is the fact that its relative insolubility leads to its being precipitated as uric

acid; all urines, if they are prevented from decomposition, precipitate uric acid sooner or later, in health or in disease; but in health the precipitation of uric acid—that is to say, the conversion of the quadriurate into uric acid—does not occur within any short time of the urine leaving the body, sometimes it is twenty-four hours or longer. If the ordinary urine is left in the air, ammonium carbonate is formed, and then you have urate of ammonia, and the precipitation of uric acid does not occur. In certain diseased conditions the urine deposits uric acid very much sooner, and, in fact, sometimes the urine deposits uric acid before it has left the pelvis of the kidney, so that you have a stone in the pelvis of the kidney, or you may have a stone in the kidney, or the precipitation may occur a few minutes after passing the urine. In health, as mentioned above, this condition does not occur till a considerable time has elapsed after passing the urine. In disease the conversion of quadriurate into free uric acid occurs sometimes before the urine has left the kidney or the bladder, and the patient then runs a considerable risk of forming a urinary calculus or renal calculus; and I may as well say that most cases of stone in the bladder arise secondarily to stone in the kidney, first of all there is a small stone in the kidney, and that passes into the bladder and forms the nucleus for a second or larger stone. What are the conditions which will lead to the formation and precipitation of uric acid?

First of all you have to consider the amount of uric acid. It is a platitude to say the more uric acid there is in the urine the more likely is this change to occur, that is self-evident, and to people who have this abnormal tendency a large meat diet is injurious; but there is a point about a large meat diet which is sometimes forgotten. A large meat diet may lead to precipitation of uric acid simply on account of the presence of phosphate of soda in the meat; the acidity of meat is also partly due to lactic acid, but a meat diet renders the urine acid owing to an increased excretion of acid phosphate of soda. Thus an excessive meat diet may affect the uric acid in the urine by increasing the amount excreted, or indirectly by affecting the acidity of the urine by increasing the acid phosphate of soda. If the urine is acid, this breaking up of the quadriurate occurs with much greater rapidity; in the normal urine it does not occur rapidly, because the normal urine contains a lot of salts; but if it contains acid salts, the urine acts practically like water, and splits up the quadriurate, and that is the real reason why the starving urine before breakfast is most apt to deposit uric acid, it is the urine of the metabolism of the tissues unaffected by diet. The urine before breakfast is passed at a long interval after meals, and is very acid, and therefore it is the urine most prone to deposit uric acid.

The proper way to treat a patient with gravel is to give a large dose of citrate of potash when the

patient goes to bed, so as to render the morning urine as alkaline as possible, and order him a suitable diet during the day to render the diurnal urine less acid or alkaline. The next thing that helps the precipitation of uric acid, apart from the amount of acid present, is that the more dilute the urine or the more scanty the presence of salts, the greater the tendency to precipitation, and it is well known that the urine of granular kidney is a urine that tends to deposit uric acid. That little point will show you that the question of the dilution of the urine is at any rate of equal importance with the quantity of uric acid present. In pneumonia, where a concentrated urine is passed, the amount of uric acid is considerable, it all passes out as urates, and is therefore soluble. . Take, on the other hand, a patient with granular kidney, whose urine is very dilute, with very little uric acid, and yet that patient may deposit enough uric acid to give him serious trouble in the way of gravel or even of stone. There is another thing that influences the precipitation of uric acid, and that is the amount of pigment present in the urine. These are the main points of interest; and when you think that gout and gravel practically depend on the conversion of quadriurates on the one hand into acid urate of soda, and on the other hand into free uric acid, I think you will admit that it is of importance. There are few diseases which can be explained satisfactorily; scabies is one, and gravel and the formation of tophi in gout are

others. No one can say with certainty why a person with gout has an excess of uric acid in the blood, but given that condition one can explain the rest of the phenomena. There is an interesting corollary ; no one has ever heard of a patient suffering from an attack of gout and gravel at the same time, although of course a person with gout is liable to gravel ; but you never have a person with a paroxysm of acute gout passing gravel at the same time, and when you see that gout is due to the presence of an excess of uric acid in the blood, and gravel to the precipitation of uric acid in the urine, you can understand why you do not have the two things occurring together.

Do not forget that uric acids, and urates, and creatinin have the power of reducing copper ; it is not limited to creatinin. As regards the test for uric acid, clinically one relies practically on the crystals ; one is not in the habit of doing the chemical tests, and there is not much to be said about the crystals ; if you want to get the crystals, you add some hydrochloric acid and keep the urine for twenty-four hours, under these circumstances it crystallises out, and one of the characteristic facts is that the crystals are coloured, and they are coloured by the uroerythrin ; pure uric acid is of course colourless, and it crystallises in flat colourless plates. If you want to prepare the pure specimen you must prepare the impure form first, and then dissolve it in some alkali, and then re-precipitate it again. If you take crude uric acid and dissolve it

up in an alkali, and then recrystallise it, it does not crystallise in the well-known spindle-shaped coloured form that every one is familiar with, but it crystallises in these flat colourless plates.

Occasionally acid urate of soda and acid urate of ammonia are formed in children; these are not present in normal urine, but in children's urine these two salts are sometimes formed, and these bodies crystallise, forming so-called hedgehog crystals,—a round central body with spikes sticking out. The delicate urethra of children is liable to be injured by these prickles, and they will sometimes cause retention of urine; they irritate the urethra and cause a spasm of the urethra, and it is a condition easily put right by giving an alkali: it is not of any importance in adults.

As regards *urea*, urea is of comparatively little importance; I suppose it is somewhat of a heresy to say this, but though urea is of course of great scientific importance you do not arrive at very great diagnostic results by studying the excretion of urea in the urine. Urea is affected enormously by diet; the thirty grammes that we usually pass, although this amount is liable to considerable variations, is mainly derived from the food. If you examine the urine of a starving patient—ovariotomy patients are usually starved for a day or two, and they are very frequently comparatively healthy people except for the presence of the tumour—you will find that they do not pass more than ten or twelve grammes of urea in the twenty-four hours.

It is very unfair to take the thirty grammes as the amount of urea that a hospital patient ought to pass; thirty grammes is what a healthy person should pass. If you lie in bed all day on a scanty diet you are pretty sure not to pass thirty grammes of urea; therefore, if a patient does not pass thirty grammes in the twenty-four hours you must not assume that there is anything very seriously wrong with him; thirty to forty grammes is the amount for a healthy person, and is not the amount for a patient lying in bed on a sick diet. On the other hand, the appetite fails in most diseases, and hence a patient who is passing as much as thirty grammes may be losing much of his nitrogenous tissues; it is quite possible he is eating very little, therefore the estimation of urea is useless unless you know what the nitrogenous intake is.

VI.

I POINTED out to you last time that the amount of urea that patients pass was largely dependent on diet, and that a patient may pass a small amount of urea and yet that this may not signify because it may be due to a limited diet. Further, that a patient may pass only a normal amount of urea,—thirty grammes,—and yet there may be extensive wasting going on, and the deficient urea excretion is dependent on the patient taking little or no food. There is only one class of disease where it is really important to determine accurately the urea excretion, and that is in certain renal diseases, more particularly Bright's disease, and the diseases where the kidney substance is atrophied, as for instance in cases of so-called surgical kidney, and in cases of hydronephrosis and cystic kidneys. The current text-book teaching on the subject is that a diminution in the excretion of urea in renal disease is very serious and betokens the onset of uræmia, and of course no doubt to a certain limited extent this is true; but I can only repeat that if you have a patient with renal disease who is only passing fifteen to twenty grammes of urea, you must remember that there are many causes to account for that, quite apart from the small urea

excretion being due to any imminence of the onset of uræmia. A patient with Bright's disease eats very little, also he is often very sick, and hence they really assimilate still less than they eat, and then a patient with Bright's disease probably has a considerable amount of albuminuria; all these three things—diminished food, the repeated vomitings, and the albuminuria—will very largely tend to diminish the nitrogenous metabolism of the body. Then in addition the patient with Bright's disease may have profuse diarrhœa, and when there is profuse diarrhœa there is of course a very considerable loss of proteid matter in the intestinal flux. And lastly, a patient with Bright's disease is very often dropsical, and when you remember that the percentage amount of urea in dropsical exudations is as great as it is in the blood, it is often impossible for the patient with Bright's disease to pass anything like the normal quantity of urea, perfectly impossible, so that you must not jump to too hasty conclusions because the quantity of urea is diminished in certain forms of Bright's disease. Uræmia must not be considered imminent simply because there is a scanty urea excretion. But there is no doubt that a permanent scanty excretion of urea is a matter of some gravity. In certain other diseases, more particularly in cases of so-called surgical kidney, where the kidney lesions supervene on the top of strictures of the urethra or enlarged prostate and various other impediments to the exit of urine, in

such cases you may often gain valuable information as to the state of kidney by examining the urea excretion, and in these cases the percentage of urea may be very low; instead of 2 per cent. there may be only 1 per cent. or even less. The same remark applies to some cases of hydronephrosis; in uterine cancer, for instance, pressure on the ureters will cause hydronephrosis, and the long-continued excretion of a dilute urine containing a low percentage of urea suggests the presence of considerable structural alterations in the kidney, and this is more especially characteristic of surgical kidney and of hydronephrosis. These conditions are liable to be overlooked, the symptoms are often not prominent, and hence the percentage of urea in these cases may be a useful physical sign if looked for. If you are going to determine the amount of urea in the urine, it is waste of time to examine a sample; you must mix up the whole twenty-four hours' urine, otherwise you may have the most fallacious results.

There are certain diseases in which the excretion of urea is very greatly increased, more particularly, of course in diabetes. This is a disease in which the excretion of urea is much increased, and the increase is mainly due to the increased appetite, and to the fact that the diet is generally exclusively an animal one. Pathologists have supposed that the increased excretion of urea in diabetes is dependent on the disintegration of the proteids of the body. Of course it is to a certain extent so, for these

patients waste largely; but in many cases the increase of urea is due to the large appetite of these patients. It has also been suggested that in some cases diabetes is a disease of the muscles, the muscles breaking up into a carbohydrate moiety which is excreted as sugar, and a nitrogenous moiety excreted as urea.

In diabetes insipidus the amount of urea is rather large, but the percentage is very low. Patients with diabetes insipidus may pass an increased amount of urea, but the percentage is always very low, since it is not unusual for these patients to pass some twenty pints of urine. There is another condition which is rather obscure, and I should not like to say that it is definitely established, but it has been thought probable by many, and asserted positively by some, that in the true granular kidney there is an increased excretion of urea in the early stages of the malady; it is one of those things that is very difficult to prove. It is known that the initial symptoms of patients with granular kidneys are sometimes not renal, they do not come with obvious renal symptoms such as headache, vomiting, &c., they come with general weakness and emaciation, they may even have a fair appetite, of course later on that fails; but in the early stages of the disease or in certain periods of the disease, patients with granular kidney suffer more from general nutritional disorders, loss of strength and wasting, and along with these it is asserted that there is an increased excretion of

urea. It is, however, quite certain that patients with advanced, I mean very advanced renal disease, who only have a few weeks or months to live, sometimes pass large quantities of urea. I remember myself a case very well in which I carried out a complete series of investigations on the nitrogenous metabolism, and that patient passed for weeks and weeks a daily average of forty grammes of urea. So that although, broadly speaking, in renal disease the urea excretion may be diminished, yet it is not really definitely shown that the diminution in the excretion of the urea is always due to impaired excretory activity of the kidney. It is often due to want of food, and to rejection of food, and to albuminuria and so forth, and certainly in some advanced cases of renal disease a patient may pass quite large quantities of urea.

Urea is of very little clinical importance apart from these facts. There is, however, one further thing to note, and that is the diminution or disappearance of the urea in the urine in certain grave diseases, and more especially in acute yellow atrophy of the liver. You may go many years without seeing that disease, although we have had several cases here; but it is not seen very often, and some physicians absolutely refuse to recognise it. Acute yellow atrophy is a disease (of course I am giving you a cut-and-dried statement) in which the liver cells undergo degeneration *en masse*, and great areas undergo necrotic changes; it is so rare that some physicians do not believe in it, but I

think there can be no doubt about the existence of the disease. But there is another condition which resembles it. When I was a house physician in this hospital, I saw several cases of phosphorus poisoning, and phosphorus poisoning produces very similar changes in the liver to acute yellow atrophy, and phosphorus poisoning is sometimes not detected unless you inquire particularly for the possible poisoning. A former student, when taking a *locum tenens*, had a curious example of this. Some people had got up private theatricals, and there was a ghost in these theatricals, and the girl who took the ghost's part covered her face and arms with some phosphorus paste; this was all forgotten after it was done, but some time afterwards this girl began to get very ill, and she died of phosphorus poisoning, and it was only discovered by close questioning how this phosphorus poisoning had been produced, and if she had not been examined so closely and accurately that case would have been undoubtedly put down to acute yellow atrophy of the liver. You will also see cases of women with a history of abortion followed by acute yellow atrophy. Many of them are connected with illegitimate child-bearing, and it has been suggested that this acute yellow atrophy in connection with the abortion is sometimes due in these cases to phosphorus poisoning. In various grave diseases of the structure of the liver, more particularly in cirrhosis and obstruction of the bile-ducts, you get what the Germans call secondary

acute yellow atrophy; that is to say, after the long continuance of the cirrhotic changes or long-continued obstruction of the bile-ducts, the liver cells undergo a somewhat similar change to that seen in acute yellow atrophy, and the patients suffer from cholæmia, that is to say a condition of coma due to a toxic agent, and liable to occur as a terminal phenomenon in such cases of liver disease. This secondary acute yellow atrophy is by no means uncommon, the primary atrophy and the yellow atrophy from phosphorus poisoning are uncommon. The last is uncommon now because amorphous phosphorus is more used in the manufacture of matches. In acute yellow atrophy the urea excreted diminishes greatly, and it may disappear altogether. Leucin and tyrosin occur in the urine. This fact is often regarded as evidence that the liver forms the urea, because in the condition in which the liver practically becomes non-existent leucin and tyrosin appear in the urine instead of urea; that to my mind is very slight evidence that the liver forms urea. In phosphorus poisoning it was said that leucin and tyrosin did not appear in the urine, but that is now known to be incorrect; in cases of phosphorus poisoning leucin and tyrosin may be present in the urine, and the urea is certainly greatly diminished. Similarly in those cases of so-called secondary acute yellow atrophy arising in the course of hepatic cirrhosis, &c., leucin and tyrosin may appear in the urine.

Urea disappears or undergoes diminution in

acute yellow atrophy, in phosphorus poisoning, and in the diseases in which the liver substance is extensively destroyed, and in these conditions lactates appear in the urine. This is a fact of some interest, and is similar to what is known to occur experimentally after the extirpation of the liver.

As regards the qualitative detection of urea, the best thing to do is to concentrate the urine and obtain the nitrate or oxalate of urea; if you want a quantitative test, everyone uses the hypobromite test. In doing that test, first of all it is necessary to work with bromine tubes and caustic soda; you cannot work with hypobromite solution, which, if it is made and kept, undergoes changes; you must make your hypobromite solution at the moment you do the test. To do the test accurately, you must measure the gas, and you must not trust to those graduated instruments for the percentages, because they are frequently wrong. When tilting the urine into the hypobromite it must be done very gradually; if you do it all at once the whole of the urea will not be decomposed. The great point, therefore, is to remember that it must be done gradually, you must be very careful that you let the hypobromite cool when you mix the bromine tube and the caustic soda; you cannot be too careful in letting it cool, otherwise there will be an error in the result. The hypobromite test is a very fairly accurate method, although it is about 8 per cent. wrong, but still, nevertheless, it is a fairly accurate method. For one thing, this 8 per

cent. error is constant, but if there be sugar in the urine this 8 per cent. error is not present; and the fact remains that sugar in the urine allows the whole of the urea to become decomposed. Hypobromite decomposes other nitrogenous bodies besides urea; it decomposes creatinin, and the various nitrogenous bodies that are present, but creatinin is the most abundant of these other substances. If you want to conduct investigations on the nitrogenous metabolism, the total amount of nitrogen in the urine must be determined, but that is not generally done. Clinically, it is usually sufficient to determine the amount of urea, but you must determine the amount of nitrogen if you wish to obtain really accurate results; Kjeldhal's method is the one most suitable for the purpose.

As regards the other nitrogenous bodies in the urine, creatinin we have considered, xanthin and hypoxanthin are of practically no clinical importance; xanthin may perhaps rarely occur clinically in large amounts, but, however, they are both pathological curiosities.

We will pass on to a very much more important subject, viz. the presence of carbohydrates in the urine. It is well to call this condition not diabetes but glycosuria; the two names are not synonymous, you may get diabetes without glycosuria, you may have glycosuria without diabetes. In a certain stage of some cases of diabetes there may be no sugar, and you can have a patient with glycosuria without the patient suffering from diabetes. The

first question as regards glycosuria is the same as with regard to albuminuria, that is whether there is any sugar in the urine in health. There has been an immense amount of controversy on this subject; but it is one of those things that is of no great importance from our point of view, clinically, because whether there be sugar in the urine or not, everybody is agreed that this trace of sugar, if present, is of no pathological significance. So that to all intent and purpose with the ordinary sugar tests, the urine normally is free from sugar, but if you ask the question scientifically there is probably sugar in the urine; you have to concentrate large quantities of urine to get the result, or to use very delicate tests. Quite apart from this question there is no doubt that the normal urine contains reducing substances, and as regards these reducing substances which may be present I have mentioned uric acid, and I have mentioned creatinin; in addition to these you have a carbohydrate acid that is known as glycuronic acid, which is probably always present in traces as far as we know, and which in certain conditions is very much increased, and this acid is a reducing body, although it is not sugar. The amount of glycuronic acid is increased after the administration of camphor and other drugs, and its presence in the urine was first determined after the administration of this body and of chloral. The question as to whether the normal urine contains sugar, narrows itself down to whether the urine contains sub-

stances that will ferment, or will crystallise with phenyl-hydrazin. It is an experiment about thirty years old, that if you concentrate the urine you can get out of it a reducing sugar, but it is really of no great practical importance. Putting all that aside, there is unfortunately, because it complicates the subject, there is unfortunately a condition somewhat similar to so-called physiological albuminuria; that is to say, there are certainly patients who pass appreciable quantities of sugar in their urine, these people being as far as can be determined healthy. I may as well say at once, to avoid any misconception, that the more strict insurance offices will not accept lives on the usual terms when the urine contains sugar, even if the people are apparently in perfect health. So that most observers are inclined to look on glycosuria as more serious than albuminuria, but whether that rests on any sound evidence or not is another matter. As regards those persons who pass a small quantity of sugar in health, you see it principally under two conditions. First of all, after diets rich in carbohydrates, there are certain people who will pass a small quantity of sugar after eating largely of carbohydrates, they pass no increased quantity of urine, and they are apparently healthy. There is another group of cases in which a person passes sugar in his urine after moderately severe exercise. I have only seen one case; the patient was a student here, who found that he had sugar in his urine after a ten mile walk. It was

tested quite accidentally; he was going to have his life insured. It is very difficult to say whether these people who pass sugar in their urine after a meal or after exercise are slight cases of diabetes or whether they are not; they are not perfectly sound of course, there is no doubt about that, but whether they are people who will die of diabetes or whether they will live as long as anyone else is really a question that one cannot answer; the fact remains that you cannot pass them as healthy people for insurance purposes.

The next point is that you must not say that a person has got sugar in the urine simply from having noticed a reducing body in their urine. You must never say that a person has sugar in the urine simply on the basis of the copper reduction test; you must always ferment it, or use some other equally good test. The fermentation test is a good one for the purpose of a control test.

Pathological glycosuria is a large subject. First of all, one would say that there are at least three types of diabetics. First, there is a type every one is familiar with, the urine is increased in quantity and contains sugar; it not only contains sugar, but it is greatly increased in quantity. In the second place is a class of cases in which the urine contains sugar, and it is not increased in quantity, or rather not largely increased in quantity. In both these classes the specific gravity of the urine is raised, so that it is probably somewhere between 1030 and 1050. The third class of cases is that

in which sugar is present in the urine, but the specific gravity is lower than normal. You may have sugar in the urine with specific gravity of 1010. In the first group of cases the urine may contain large quantities of sugar, and the condition is often serious; the colour of the urine is altered, and it often has a peculiar greenish opalescent colour. In the second class the colour is not profoundly altered. In the third class of case the urine is pale coloured, as would be expected.

In diabetes mellitus the sugar present is dextrose, and this is a point of some pathological interest. As regards the amount, you may have up to a couple of pounds in the twenty-four hours; the most I have seen has been one and a half pounds in the twenty-four hours; it is not at all uncommon for the patient to pass one pound of sugar in the urine for months and months, so that the amounts of sugar that are lost in this way are very considerable. Then the percentage of sugar is anything up to about 10 per cent. The amount of sugar in the blood normally is in the second place of decimals; it is usually estimated at ·09 per cent., that is supposed to be about the maximum, the minimum is ·05 per cent., so that there is roughly speaking about four or five times as much sugar in the blood as there is urea, because the percentage of the urea in the blood is about ·02 per cent. If the percentage of sugar in the blood rises even slightly you get sugar in the urine, and if it rises to ·3 per cent. you get marked quantities of sugar in the urine.

We have considered the types of urine, and we have also considered the amounts of sugar present in the urine in diabetes mellitus; and now we will consider the other conditions in which sugar is found in the urine; larger quantities are found of course in diabetes than in any other condition, and the first question is whether you ever have sugar in the urine apart from diabetes. That was more easily answered a few years ago than now; one used to teach that you got sugar in the urine in a large number of cases: first of all, after injuries of the head; secondly, after a number of drugs of which opium, morphia, chloral, and chloroform were the principal; thirdly, after, or as the accompaniment of certain inflammatory diseases of the brain, more particularly meningitis; and fourthly, in any conditions such as cerebral hæmorrhage, particularly infra-tentorial, either in the cerebellum or in the pons; and fifthly, in tumours of the brain. As I say, a few years ago one said this dogmatically, now one has a certain amount of hesitation about it; it would be better to say that in all these conditions we have reducing substances in the urine, but we are doubtful whether in all cases it is sugar, after opium and chloral it is doubtful whether it is not glycuronic acid. People have relied on the copper reduction to show the presence of sugar. As regards blows on the head there the evidence is a little more clear, but no one yet has re-investigated the matter as regards the presence of glycuronic acid.

I need only say that it is a matter of traces of these substances. I can quote one case to illustrate this point. A patient in this hospital complained of noises in the ears, he had got a little deaf, and then he complained of a stiff neck, then he found that he could not pass his water properly. He still complained of the stiff neck, he was sick, and it was supposed that he had been poisoned with some ptomaine; as he was still sick and did not pass his urine he was brought into this hospital. He became comatose in the ambulance, and died a few hours after admission. That man had traces of sugar in the urine. He had an aneurysm of the basilar artery which had ruptured. It is an instance of sugar in the urine from a local increase of pressure on the medulla, and it is one of the best instances that I have seen.

VII.

Last time we saw that the sugars found in the urine are usually lactose, dextrose, and inosite, but the last is of no great clinical importance. I pointed out also the main points of so-called physiological glycosuria, and the fundamental points as regards the pathology of glycosuria, *i. e.* that it might be due to diabetes and also to various other conditions, and finally that in diabetes one recognised three fundamental classes of urine. In the first the quantity of urine was increased, with sometimes as much as 10 per cent. of sugar present, a not uncommon one; the second, where the quantity of urine was not much increased, the only departure from the normal, in fact, being the presence of the sugar; and the third where the urine was increased in quantity, and containing sugar but of a low specific gravity. Occasionally in the second class of diabetic urines you may have a large quantity of uric acid in the urine, and to this variety the name of gouty diabetes is sometimes given.

In diabetes, I think one may say, if the disease is at all severe, that sugar is not the only abnormal

substance present; you get a variety of other bodies, and more particularly compounds of diacetic acid, and very often oxybutyric acid, and occasionally acetone. The presence of acetone in the urine is not characteristic of diabetes; it is often absent in diabetes, and it is often present in non-diabetic patients. There are a large number of diseases in which you have traces of acetone in the urine. In many grave and serious diseases accompanied by marked wasting, and in febrile diseases and after the administration of anæsthetics, a variable quantity of acetone is often found in the urine. Although the name of acetonæmia is given to the toxic condition that supervenes in diabetes and causes coma, yet in this so-called condition of acetonæmia, acetone is not always present in the urine. Just as in the allied condition of uræmia the phenomena are not due to the presence of excessive quantities of urea in the blood, so in acetonæmia the coma is not due to acetone. Acetone is, however, often present in diabetic urine, and it is to this and to the salts of diacetic acid that the urine of diabetes owes its smell. These and other bodies are often present in diabetic urine, and there are certain rough tests for them which we will consider directly. I think I mentioned last time that in the severe forms of diabetes you may get even up to two pounds of sugar excreted in the twenty-four hours; under these circumstances the urine is greatly increased in quantity, and the specific gravity is high, and generally it is over 1035. I want to warn you at

the outset that you must not take the specific gravity of the urine as an index of the percentage or gross amount of sugar present. If you have two specimens of diabetic urine, one with a specific gravity of 1035 and the other with one of 1040, it does not necessarily follow that the percentage amount of sugar in the latter case is greater than in the former ; the total amount of sugar passed is of course dependent very greatly on the quantity of the urine passed. The specific gravity is not an accurate index to the percentage amount of sugar present. The specific gravity is in part dependent on other substances present, more particularly on the urea and to a certain extent on the salts and so forth ; hence with a urine containing large and variable quantities of urea, the specific gravity will be profoundly affected by it. On the other hand, with a diabetic urine, which is extremely copious, the percentage of urea and salts will be so small that the specific gravity will depend largely on the sugar, and in that case the specific gravity will give you an index to the amount of sugar present. Hence in a case of diabetes if the specific gravity diminishes as a result of treatment, that may or may not be an indication that the percentage of sugar present is less. The three main points about the specific gravity of the urine in diabetes are, firstly, that it is usually high in diabetes; secondly, that the variations in the amount of specific gravity do not necessarily vary *pari passu* with the amounts of sugar present ; and lastly, that

sugar may be present in a urine with a specific gravity of 1010.

Diabetic urine not uncommonly contains albumen, more particularly in the last stages of diabetes; one of the complications of diabetes is renal disease, and under these circumstances you have albumen in the urine, and with albumen in the urine, particularly if the amount is large, you cannot get the ordinary sugar test, and hence you may think that the sugar disappears when the albumen appears. It is really only that the presence of the albumen for some reason interferes with the ordinary sugar test; hence the rule to look for proteid before testing for sugar.

Another thing as regards the sugar of diabetic urine is, that towards the end of diabetes, particularly if the disease is fatal from coma, the sugar diminishes or even disappears, and you may have a patient dying from diabetes and perhaps for several days or even a week his urine will contain no sugar, and there may be a great diminution in the quantity of the urine. Hence the presence of sugar in the urine does not prove that the patient has the disease diabetes, since, as we have seen, glycosuria may arise from other causes, and the absence of sugar does not prove that he has not diabetes, since it may disappear during the course of this disease. In the natural course of the disease it is only at the end of the malady that the sugar may disappear from the urine. Of course you will understand that I am only talking of the

natural progress of the disease, and I am not alluding to the effects of treatment. I have known of one diabetic patient where the sugar disappeared temporarily from the urine without treatment and without coma supervening; but it is usually a very fatal sign, and the sudden diminution or disappearance of the sugar in the urine of a diabetic patient may mean that coma is imminent, and coma in diabetes is practically always fatal.

Patients with diabetes tend to have a subnormal temperature, just as is the case with patients suffering from renal disease. If a patient with diabetes contracts some febrile complaint, one of three things may happen: firstly, the onset of the febrile illness may cause the development of coma; secondly, the febrile malady may run the whole of its course without any fever; and, thirdly, during the course of the febrile complaint the sugar may diminish or even disappear from the urine. I cannot do better than call to your mind a case of Dr. Poore's. A man with severe diabetes contracted typhoid fever, and during the whole time he was feverish there was a great diminution in the amount of the sugar in his urine. This is a point of some theoretical importance; the fundamental thing in many cases of diabetes is that the excess of sugar in the blood may be due not so much to increased production as to the sugar formed in normal amount not being used up, and many persons have supposed that in ordinary diabetes the patient cannot use up the sugar that he nor-

mally makes. The fact that the glycosuria diminishes or disappears during pyrexia seems to show that this sugar can thus be used during the febrile process.

There are various grades of severity of diabetes, more particularly the following:—Patients whose sugar disappears as soon as they are dieted, the sugar disappearing as soon as the carbohydrates are withdrawn; and then you have patients in whom the withdrawal of the carbohydrates has little effect, and on whom treatment by opium has effect; and finally there is a severe form in which opium and diet have little or no influence, and these patients often pass very large quantities of sugar, and frequently are under twenty years of age.

As regards the other bodies present in the urine in diabetes, acetone, diacetic acid, and oxybutyric acid are the more important. Some say that they are only present when coma is present or imminent; but that, however, is not the case, and diacetic acid and even acetone are often present in diabetic urine without coma. For diacetic acid we have a rough and ready test with perchloride of iron, by which its presence can generally be detected. The recognition of oxybutyric acid is more difficult, because there is no rough test for that; you have to distil the urine and obtain the oxybutyric acid, and determine its melting point, and so on. There is no doubt that oxybutyric acid is present when coma is present or imminent, but I do not think that one can say that it is not

present in other conditions in diabetes when coma is not necessarily imminent.

Now as regards the tests. You have of course the qualitative and quantitative tests, and there are a large number of qualitative tests, but there are not many with which we need concern ourselves; first of all, there is the well-known copper test. I only repeat that more mistakes are made in testing for sugar than in any other form of test. The best way is to pour sulphate of copper into a test-tube, and then empty this sulphate of copper out; you will have enough of the salt left sticking to the tube, then put in the urine, and then an excess of potash, and then boil it. There are two precautions; one is not to have too much copper present, and the other is, to use the expression of a former professor of chemistry, "do not cook it," raise it simply to the boiling point. If the urine is boiled a long time, almost any urine will give a slight reaction; simply raise the fluid to the boiling point. Supposing the urine contains but little sugar, if you boil the urine with an excess of copper sulphate you may get some black oxide of copper formed, and under these conditions you cannot tell if sugar is present or not. The object of only raising it to the boiling point is that uric acid, urates, and particularly creatinin, have a slight reducing action on copper, but which is not marked unless the urine be boiled for a long time. If you take any dense febrile urine and boil it with copper and potash you will get a

spurious reduction. Fehling's solution is a more convenient method for performing the same test; in this reagent, the hydrate of copper is kept in solution by the tartrates in the Fehling's solution. The objection is that Fehling's solution does not keep, and you ought to take the precaution of always boiling it by itself first of all to see that it does not reduce. Take a big test-tube and boil thoroughly the Fehling solution, it does not matter how long you boil that; you add to that preferably one or two drops of the urine, do not add too much because an excess cools down the boiling mixture. If there is an appreciable amount of sugar present, the reduction occurs at once; if there is only a small quantity of sugar present, you do not get the reduction for a few moments; if there are only traces, it may be necessary to add more than the few drops of urine, but under no circumstances add more than half a volume. If you add these larger quantities of urine you have to raise the fluid to the boiling point again.

There is the well-known potash test, the so-called Moore's test, in which on boiling the urine with potash the liquid becomes brownish-red in colour, varying from a pale sherry to a dark mahogany colour, depending on the amount of sugar present. It is a very good test, but not so delicate as the copper test.

There are a large number of other tests, for instance the picric acid test. I think this test has this advantage—it is a test for albumen and for

sugar, and the presence of the albumen does not interfere with the sugar test. You take your suspected urine, and add some saturated solution of picric acid, and add some potash, and you warm it; if sugar is present you get a very deep blood-red colour, but the fallacy of the test is that every urine gives a red colour with picric acid and potash; and it is simply a question of the depth of the colour. It is not a question of the colour alone, for creatinin gives the colour; therefore you must do a control test with a urine that does not contain sugar. In the hands of experts it is a very good test, but for everyday purposes it is not to be recommended, for if you rely on it exclusively you will no doubt one day find sugar where no sugar is present. The phenyl-hydrazin test is far less used now than it used to be; there are two reasons for that: in order to do it properly you have to do it with a water bath, and it takes time, and when you do it properly it is, if anything, too delicate. It is a test which is useful in testing for traces of sugar in normal urines. Hence the phenyl-hydrazin test, though a very excellent test, is not a test that is really of any very great practical importance.

There is another very good test for practical purposes. It is a bad test for determining the amount of sugar, but it is a very good test for determining that sugar is present—I mean the fermentation test. The copper test comes off with a number of bodies which are not sugar, whereas the fermentation test does not. You simply take

a test-tube, fill it absolutely full with the urine, put a little piece of yeast into it, turn it upside down, preferably over a vessel containing a little mercury, or over a little vessel containing the same urine, and then you put by the side of it a test-tube similarly arranged, and containing some urine without any yeast; put it in a warm place, preferably a warm chamber, and gas accumulates at the top of the test tube. It is a useful test in cases of doubtful glycosuria; a patient comes to you with vague symptoms, and on boiling the urine you get a sort of a reduction, say a greenish-red colour, but you do not feel sure if it is or if it is not sugar, and you think perhaps that it may be uric acid, or creatinin, or what not, and under these circumstances the fermentation test is useful to satisfy your mind as to the presence or absence of sugar, but it is not so useful to determine the amount of sugar. It can be used for that purpose; you can put some yeast into the urine, and take the specific gravity before and after, and then there are tables which will give you the amount of sugar for each unit of specific gravity lost. There are plenty of circumstances under which you may be able to ferment the urine when you may not perhaps be able to procure Fehling's solution.

As regards the fallacies, there are two sets; you may find sugar when it is not present, and you may fail to find sugar when it is present. The first is the more common. First of all there are drugs,

more particularly the salicylates, which are excreted in the urine in the form of salicyluric acid, and that body reduces copper; salicylates and salicin are taken largely nowadays. That is the drug on the whole that you are most likely to come to grief over. Glycuronic acid, a body normally present in the urine in combination with various aromatic bodies, reduces copper. There are a large number of aromatic bodies excreted in the urine; they are in combination with sulphuric acid or with glycuronic acid, and under certain circumstances, more particularly after the administration of camphor and chloral, the amount of glycuronic acid is greatly increased, and glycuronic acid gives a very perfect sugar reaction, and you can only diagnose between this and dextrose by the fermentation or by the phenyl-hydrazin test. Urates and creatinin in highly concentrated febrile urines may prove a fallacy by your having too much urine in the tube, and heating it too long. If you follow the rule of not giving a definite opinion until you have fermented the urine, you will not go wrong in these cases. As regards not finding sugar when it is present in the urine, the principal error is the presence of albumen interfering with the sugar test, and it is an error which may be avoided by testing for albumen first.

As regards the estimation I am not going to describe fully the process, I only want to mention some of the pitfalls. The estimation of the quantity of sugar is not an easy thing to do correctly,

simply largely owing to the fact that men are not told the possible fallacies. In doing a quantitative estimation, supposing you use Fehling, the following are the main points:—You should take your quantity of Fehling's solution, and that you should dilute very freely; take your 10 c.c., dilute it freely, —usually it is diluted to 50 c.c.; you must freely dilute your urine also, because the amount of sugar may be very great in the urine, and a drop from the burette may be too much at a time. You cannot, as a rule, determine the amount of sugar correctly by doing a single estimation. If you are given a urine to examine, you must make at least two determinations, and you must therefore boil up your Fehling and run in your diluted urine rapidly; the essence of success is to do the thing quickly, you run it in rapidly; if you have no idea as to what the amount of sugar in the urine is, you must run it in in quantities of 2 or 3 c.c. If you have run in say 30 c.c. you take a fresh lot of Fehling and start again; you run in 20 c.c. at once, and then only small quantities, and then perhaps you may hit it off to within a c.c. But it is absolutely impossible to do a sugar estimation with a single observation. If you try to do it as most men do, this is what happens—the urine is run in in small quantities; a considerable amount of time is taken up in the process, and the blue colour returns to the liquid on cooling. Further quantities of the urine are run in, and so on, and ultimately an extraordinary result is obtained. It is

not so simple to determine when the blue colour goes. It is often really very difficult. If you want to determine it, you must briskly boil when the urine is run in, take the lamp away, the precipitate subsides, and then tilt the dish; if it is only carelessly warmed you have to wait for the precipitate to subside, and you get the most extraordinary results. If you allow the liquid to cool the blue colour comes back, and so it goes on, so that the essence of success is to have the Fehling briskly boiling, to run the urine in very quickly, not to delay matters, and then to observe the presence or absence of the blue colour almost at once. When Mr. Gerrard was the dispenser at this hospital he introduced a modification of Fehling's solution, containing cyanide of potassium; it was really a very good method indeed, as far as I know. Owing to the presence of the cyanide no red precipitate was formed, and the end of the reaction was shown by the disappearance of the blue colour from the liquid. The difficulty arises from the conflict of the red precipitate and the blue colour.

You can form no opinion on a diabetic case as regards either its severity or the effect of treatment unless you make a routine of doing a quantitative estimation of the sugar daily. If you are going to quantitatively estimate the sugar you must have a twenty-four hours' urine—that is a *sine quâ non*. As regards lactose, this sugar is present in the urine of suckling women; it is only of theoretical

importance, and it does not ferment with yeast, so you can detect its presence by the phenyl-hydrazin test. As regards the other bodies in diabetes, acetone and diacetic acid and oxybutyric acid, we will take them in that order. Diacetic acid is recognised by the red colour it yields with ferric chloride. Take one drop of the ferric chloride and add it to a large quantity of the urine; a precipitate of ferric phosphate falls, and the urine assumes a reddish or mahogany colour: that is not due to acetone, it is due to diacetic acid. The best way to detect acetone in the urine is to make iodoform, and the simplest way of making iodoform in order to determine the presence of acetone is to use a drachm of liquor potassæ, and dissolve in it twenty grains of iodide of potassium; boil it in a test-tube thoroughly, float on to the top of it from a pipette about an equal quantity of the urine. If any appreciable quantity of acetone is present you have yellow crystals formed at the junction of the two liquids, viz. iodoform. The ferric chloride test comes off in a very large number of diabetic urines, but the acetone reaction does not come off in such a large number. Oxybutyric acid is of no great clinical importance, because there is no ready method of detecting it. You must pursue a more or less elaborate distillation of the urine and collect the distillate, and separate the acid and observe its melting point. The main interest of this body is that a considerable number of observers consider that coma is due to the

oxybutyric acid. It has long been known that the urine and even the blood of diabetic patients may be highly acid, so that the main importance of it is rather from that point of view than from a clinical point of view, inasmuch as there is no rough test to detect its presence.

VIII.

Salts of the urine.—The most important of the urinary salts are the chlorides, the sulphates and the phosphates; the urates we have already considered, the other salts are not of any very great practical importance, with the exception perhaps of the oxalates. There are minute traces of other salts present, but they are not of sufficient importance to detain us. The salts of most clinical importance are the phosphates and the oxalates; the chlorides and the sulphates are not of any great clinical interest, and this perhaps more especially applies to the sulphates. The chlorides are very abundant, and are readily detected, but the physiology and the pathology of the chlorides is very little understood. The bulk of the chlorides in the urine is derived from the chlorides of the food, but not entirely so; and the chlorides undergo in disease, more particularly in febrile diseases, changes leading to a very great diminution in the amount excreted, and that is not altogether a question of diet. It used to be taught that pneumonia was characterised by diminution in the chlorides in the urine, but it is not characteristic of pneumonia, it is really more characteristic of a high temperature. A patient

with pneumonia has a very remarkable temperature chart; the temperature will reach 104° or 105° in under twenty-four hours, and it will remain at this height, with very slight oscillations of perhaps not more than one degree, and under these circumstances the chlorides undergo a noticeable diminution. Tonsillitis, especially some of the varieties known as hospital throats, is also characterised very often by high temperature—105° is not an uncommon temperature, and it is not at all uncommon to get great diminution in the chlorides in this disease. Pneumonia is perhaps a little peculiar, because the diminution is greater in amount than in the other febrile processes, but this diminution is not characteristic of pneumonia. It used to be said when I was a student that it was one way of diagnosing pneumonia; in pneumonia the physical signs may not be shown for four or five days, therefore you may be in some doubt as to the nature of the febrile illness, and it was thought that the examination of the urine afforded a means of confirming the suspicion you might form with regard to the nature of the disease. You took the suspected urine, and you also took a normal urine, equal amounts in two test-tubes, and you took a stick of nitrate of silver and dipped it in both. In one you would notice a dense, very flocculent precipitate; in the other you would have a faint cloudiness only. But this is not of sufficient importance to detain us long. There is one point which is of importance; there is a

great deal of evidence that if you have a diet which is deficient in chlorides, and hence the urine is scanty in saline ingredients, the uric acid is liable to be precipitated, and that is perhaps the most important point about the chlorides in the urine. A high percentage of salts, not limited to the chlorides, is necessary in order to keep the uric acid normal in the form of quadriurates, and a diet scanty in saline ingredients is held to be a predisposing cause in causing uric acid calculi. It has long been known that stone is common in India, and the same remark applies to certain parts of China; at least, so it is said. In both of these countries the formation of the uric acid diathesis cannot be held to be due to an excess of nitrogenous food, because in India the diet is largely carbohydrate, and it has been shown that such a diet as this contains relatively small amounts of saline ingredients. The same thing has long puzzled people in this country. It is the experience of most lithotomists that more stone appears in children in the hospitals than in private practice; and Sir Henry Thompson, who had an almost unrivalled experience in the matter of stone, had only seen very few cases of stone in children in his private practice. Children in private practice are more likely to be better fed, hence it has been a puzzle why stone is more common in the hospital patients who are poorly fed, and the same explanation has been given: these children live on tea and bread and butter; in London they

do not get much milk, and not much in the way of proteid food, tea and bread are the staple articles of diet, and the amount of saline material ingested is scanty; and I pointed out to you when discussing uric acid, that a meat diet is not only rich in nitrogenous material, but is rich also in saline material, both phosphates and chlorides, so that the chlorides may undoubtedly play an important part indirectly in that way, in keeping up a high percentage of saline material in the urine, and in that way keeping the urates in solution.

One does not know any sound explanation of the reason for the diminution or even the disappearance of the chlorides in the urine in febrile states. There is no satisfactory explanation, and I do not waste your time over the cut and dried explanation which says that the chlorides are not in the urine, because they are in the exudation in the lungs in pneumonia. In fact, there is really no satisfactory explanation to be offered. The sulphates, I think I may say, are of practically no clinical importance, but there is a good deal of scientific interest about them. Sulphur in the urine, as you probably know, is excreted in three forms: first of all as ordinary sulphates, metallic sulphates; secondly, it is excreted in the form of what are known as aromatic sulphates, compounds of sulphuric acid, with various aromatic bodies of the indol and skatol group,—a considerable amount of sulphur is excreted in that way; and lastly, a small amount of sulphur is excreted in the urine normally

in the form of taurin-like bodies, and the only interest of that is in regard to the relationship of the taurin group to the cystin group. There is a rare calculus formed of cystin, and cystin is altogether an abnormal substance, and is rarely met with, but it is really allied to a normal constituent of the urine, viz. the sulphur compounds of the taurin type. The sulphur of the urine, like the chlorine and phosphorus in the urine, is derived partly from the sulphur of the food and partly from the sulphur of the body, and the sulphur of the body is derived from the proteids, and hence it has been supposed that the excretion of the compounds of sulphur will be modified in conditions in which there is extensive wasting of the proteids of the body. The sulphur of the food is largely excreted as ordinary sulphates; the sulphur of the body, on the other hand, is excreted probably very little as sulphates, but largely as aromatic sulphates, and hence at one time it was supposed that the aromatic sulphates gave a clue, or index, or measure to the amount of waste of the proteid tissues of the body; but it was found that the aromatic sulphates, although in part formed no doubt by the waste proteid tissues of the body, were largely formed in the alimentary canal as a result of the putrefactive processes carried on there, or the decomposition, if you like, occurring in the alimentary canal during the progress of digestion according to some physiologists; or according to others this decomposition is due

to the activity of the microbes normally found in the intestines. There is a considerable amount of decomposition in the alimentary canal, and the aromatic sulphates are formed here. It was supposed they were formed from the proteids of the body because it was observed they were present in the urine even during starvation, and hence the idea that they were formed from the tissue proteids. It was shown by a man who died a short time ago, Baumann of Freiburg, that in starvation you get what are called artificial fæces; you have an exudation into the lumen of the intestine from the blood-vessels of the intestine, and this exudation contains proteid matter, and therefore it is quite possible that even the aromatic sulphates of starvation have largely an intestinal origin. These aromatic sulphates are undoubtedly formed in the intestine, even when no food is taken, but it is possible that they are also formed by the breaking down of the tissues in the body at large; and of course there is a well-known physiological fact, a well-known experiment of Bunge, that animals fed on proteids deprived of salts (mice fed on casein, having had the lime washed out of it) will die more quickly than if they are starved. Death occurs sooner than if they are starved when they are given food without salts; and Bunge held the view, and adduced evidence in favour of the view, that this was due very largely to the formation of sulphuric acid with no inorganic material present to neutralise this powerful acid. It is definitely

proved that aromatic sulphates are formed in the intestine, and it is probable that they are formed by the breaking down of the proteid tissue in the body; it cannot be said that they are formed away from the intestine; it is possible that even in starvation the exudation in the intestine (the artificial fæces) is responsible for the formation of these aromatic sulphates. In health, aromatic sulphates exist in about the proportion of 1 to 12; that is to say, of every 13 parts of sulphuric acid in the urine about 12 parts are excreted as ordinary sulphates, and about 1 part is excreted as an aromatic sulphate. Personally, I always impress upon you the point that the excretion of these aromatic sulphates in the urine is a very curious phenomenon, and shows the relation of the kidney to the alimentary canal. You might have thought that these bodies would have been evacuated by the rectum; instead of that they are re-absorbed and excreted by the urine. The kidney actually excretes material formed in the intestine and absorbed from the intestine, and therefore when the function of the kidney is compromised and excretion is impossible, it is quite possible that the patient will succumb to intestinal poisoning. That is a theory that has been held as regards uræmia, and it is a theory that you cannot dismiss in a few words, because normally it is evident that the kidney does do such work. The amount of aromatic sulphates is a measure of the amount of intestinal putrefaction and of tissue disintegration;

and the former is more important because the latter, as I have hinted, is by no means so conclusively proved as the former.

In all conditions in which intestinal putrefaction is increased the aromatic sulphates are increased; hence in all cases of intestinal obstruction or even of constipation, anything from constipation to complete obstruction, the aromatic sulphates are increased, as is also the case where there is extensive intestinal putrefaction and diarrhœa. The aromatic sulphates are also increased in peritonitis where the bowel is paralysed, and you get, as is well known, an accumulation in the lumen of the bowel of a most offensive character, a thin brownish fluid, the exact nature of which is not understood; certainly it is not simply fæcal. The urine in those cases is dark in colour from skatol and indoxyl pigments; and, speaking broadly, the aromatic sulphates are increased in all conditions where these pigments are present in the urine. You estimate these aromatic sulphates in the following way; it is not a matter of very much trouble, or of very much clinical importance. You boil the aromatic sulphates with hydrochloric acid, and they are converted into ordinary sulphates,—that is the first point. The second point is that an aromatic sulphate does not form an insoluble precipitate with chloride of barium; and the estimation is based on these two points. You take 100 c.c. of urine, and you add to that an equal volume of a solution of barium chloride and barium hydrate

in the proportion of 66 per cent. of the former to 33 per cent. of the latter, saturated solutions of both salts being used. All the ordinary sulphates are thrown down, and you then filter, and to the filtrate you add some hydrochloric acid and you boil it, and having boiled it smartly for five minutes you then put the boiling liquid in a warm chamber, at a temperature of about 100°, for two hours, and thus the aromatic sulphates are converted into ordinary sulphates and precipitated. To estimate the total sulphates you simply take 50 c.c. of the urine and add hydrochloric acid and boil it, and add some barium chloride, and that throws down the sulphates, and then compare the weights obtained in the two experiments and you get the relation between the ordinary and the aromatic sulphates. In diseased conditions the proportion rises considerably. It is more a method of scientific interest than of practical importance.

IX.

THE phosphates are the salts of the urine which are of most importance clinically, and the phosphates in the urine (we must repeat what we have said about the sulphates and chlorides) are mainly from the phosphatic material in the food, and partly from the tissues in the body; but many persons with a smattering of chemistry think that the phosphates of the urine are derived mainly from the tissues of the body. The amount of a phosphatic deposit in the urine is no index to the amount of phosphates actually present. The phosphates present in the urine may be divided into two groups; there are the earthy phosphates and the soluble phosphates. Phosphate of soda is the typical representative of the one, and phosphate of lime is the typical representative of the other; phosphates of magnesium and phosphates of soda represent the soluble form, and phosphate of lime represents the insoluble. It is useless to make any observations on the amount of phosphates in the urine, except with the uranium nitrate method, which estimates all the phosphates present.

There are two points to be considered about the phosphates, firstly the amount of phosphates in

the urine, and secondly the mode of their excretion, and in this respect the phosphates resemble the urates. When we were doing the urates, you will remember I said that the mere amount of uric acid is often of secondary importance. The main point is often the condition determining its deposition, and the percentage amount of uric acid in the urine is only one determining factor. So it is as regards the phosphates; the question of practical importance is what are the conditions which lead to the deposition of the phosphates in the urinary channels, and in these conditions very often the amount of phosphate in the urine is the least important, so that the long and the short of the whole matter is, that the quantitative determination of phosphates in the urine is but rarely done. The thing to study is, what are the conditions which lead to the deposition of phosphatic material in the urine?

The solubility of the salts of phosphoric acid, particularly of the lime salts, depends on the nature of the salts, whether mono- or di- or tricalcic salts—the tricalcic salts being very insoluble, the dicalcic salts being more soluble. The question of the solubility of the phosphates in the urine is very largely a question of the reaction of the urine, and you will remember that urine if it is alkaline may be made alkaline owing to the presence of volatile alkalies or owing to the presence of fixed alkalies. Every one knows that decomposing urine becomes muddy owing to the

precipitation of phosphates, and the phosphates that are thrown down under these circumstances are the triple phosphates, that is to say the ammonio-magnesium phosphates; that is a condition which occurs in urines exposed to the atmosphere, and undergoing decomposition. That may occur in the pelvis of the kidney as the result of pyelitis, or in the bladder as the result of passing a dirty catheter. If an organism that decomposes the urine is introduced, you will have ammonio-magnesium phosphate formed; it is a crystalline deposit, and it has a great tendency to form a stone, but rarely in the kidney, more frequently in the bladder, and here the stone is usually formed by phosphatic deposition around a nucleus of some other material, *e.g.* uric acid. The fixed alkali will lead to the precipitation of the earthy phosphates in an amorphous form; this condition we all of us have at times, if you watch your urine you may observe it two or three hours after meals. There are very few people who do not occasionally pass milky urine from the precipitation of phosphatic substances. Nervous individuals notice this milkiness, and consider it due to the passage of seminal fluid, or else think it due to phosphatic material derived from the metabolism in the body; they get into the hands of unscrupulous persons, and they may become very ill from hypochondriasis and other allied ailments. It is a condition that is seen in very slight departures from health, more particularly in cases of slight indigestion, and that

is a condition you understand, that is not in any way due to an excess of phosphatic material in the urine; it is due to diminution in the acidity of the urine, leading to a precipitation. If you succeed in making the urine acid, the milkiness disappears. As to how the urine is best made acid the way is to alter the diet, order a diet that is relatively poor in vegetable matter; anybody who eats largely of vegetable matter is bound to get an alkaline urine with this phosphatic deposit. You should give benzoic acid or some compound such as ammonium benzoate, which is a fairly certain method of increasing the acidity of the urine; they are both very nasty drugs to take, hence they are usually prescribed in cachets. You should not try and increase the acidity by giving mineral acids, for mineral acids in large quantities tend to damage the kidney. There are several other phosphates to be considered; there is a phosphate of lime that is known as a stellar phosphate, because it crystallises in long needles, and forms rosettes, something like the rosettes of tyrosin crystals, but they are not coloured like tyrosin tufts, which are greenish, whereas the phosphatic ones are not; they are also usually bigger. I cannot tell you why these crystals form, that is not known; it is probable that the same explanation holds that holds in the case of the oxalates. You occasionally get this crystalline stellar phosphate formed in more or less normal urines, and they may give rise to trouble by the formation of a calculus. But a phosphatic

calculus is almost always secondary; it is formed in the following way generally. There is a uric acid calculus formed in the kidney, and coming down into the bladder cystitis is set up, decomposition of the urine occurs, and you have a triple phosphate deposit outside the uric acid nucleus.

There is one more point about the phosphates, viz. the confusion with albumen. When you warm urine containing only a small amount of acid, and *a fortiori* if alkaline, a cloud appears, and that cloud is a calcic phosphate. There has been a great controversy as to the explanation of this precipitate. There are the following views held with reference to this question; two of them are certainly rather doubtful, but one is obliged to mention them. It has been said that the boiling of this urine which is deficient in acid leads to the precipitation of phosphatic material, owing to the formation of ammonia from the urea. If you boil a urine that is very nearly alkaline, you decompose the urea into ammonia, and the increase in the alkalinity by the ammonia is said to be sufficient to precipitate the phosphate. When you boil such a urine you decompose some urea—Shattock showed that,—but you have to boil it for some time, and this deposition of phosphates occurs long before the urine *is* boiled, it occurs as soon as the urine is warmed; and therefore this explanation cannot, I think, be accepted, first because it requires more or less prolonged boiling to decompose the urea, and secondly because it occurs without boiling.

The second explanation was that the phosphates were kept in solution by the carbonic acid, and that on boiling, the carbonic acid was driven off, and therefore the phosphates came down; but the same thing occurs if the urine is boiled in a sealed tube. The most likely explanation is that the deposition of the phosphates on warming is owing to an interaction between the phosphates, forming the tricalcic phosphate; the cold urine contains dicalcic phosphates, and as a result of warming, two molecules of dicalcic phosphate become converted into a molecule of monocalcic phosphate and a molecule of tricalcic phosphate, and the tricalcic phosphate is insoluble, and comes down. The cloudiness appears on warming, and on being cooled again it disappears, if the test is done in a sealed tube.

We will now pass on to the oxalates. Oxalates are important, owing to the formation of calculi, the oxalate of lime calculus. The mulberry calculus is not very common; but it is a very serious form of stone, owing to its hardness, and it has led to accidents to instruments in the attempt to crush it. Oxalate of lime is also important, because you can have little minute microscopic stones causing hæmaturia. Some elderly patients will have hæmaturia, and there is little doubt that it is due to small oxalate stones. The oxalates are present in small amounts in normal urine, but certain persons apparently make more oxalic acid than others; there is apparently an oxalic acid diathesis,

as we have seen that in all probability there is an uric acid diathesis. In diabetes you may get an excessive amount of phosphates excreted, and one French observer holds the view that phosphaturia always precedes glycosuria.

Some physicians hold that persons suffering from oxaluria are dyspeptic. If you examine the urine of hypochondriacal patients, you may find traces of oxalates. The most important condition in which you have oxalates in the urine is undoubtedly as a result of eating vegetables, more particularly of coarse rhubarb. You would be surprised at the great number of persons who get rather severe symptoms from this. I have seen several cases of patients who have had severe symptoms —pain in the back and hæmaturia—as the result of oxalates; the whole thing has been produced by eating rhubarb and various other vegetables. It follows, therefore, that you ought always to think of a vegetable source for oxalates in the urine. An interesting point has been worked out with reference to the formation of calculi consisting of oxalates; we know most about it in the case of the oxalate of lime calculi. You will remember when doing uric acid I drew your attention to several conditions which tended to cause the precipitation of the uric acid, but there is always the question as to what causes the first crystal; the growth is easy to understand, but what causes the first crystal is more difficult. It has been shown in the case of oxalates that the presence

of proteid matter or even of bodies allied to proteids, mucin, influences the crystalline formation very greatly. If you take a solution of oxalic acid, and add some lime to it and get crystals formed, if you do it in an ordinary medium you get minute crystals; but if you do this in a medium with a small amount of albumen or mucin, you get much larger crystals. If you cut sections of the mulberry calculus—and there is a very interesting series of them published in the Pathological Society's 'Transactions'—you may find that the nucleus of the stone is one big crystal. It has long been known that patients with oxalic acid calculus have it often only on one side; uric acid stones are perhaps more often seen on both sides. It has been always difficult to explain that on the diathesis theory, and these observations to a certain extent do not explain it, but they throw some light on it. If a patient tends to excrete larger quantities of oxalic acid than he ought, if he gets a little pyelitis or hæmorrhage into the pelvis of one kidney, he will run a risk of forming a stone. A small amount of proteid material will influence the crystallisation to such an extent as to make a salt (which usually crystallises in small microscopical crystals that give no trouble) crystallise in such large crystals that one of these may easily act as the nucleus for the subsequent growth of a stone. This has not been shown in the case of uric acid, but a somewhat similar phenomenon is seen with this body, as in crystallising it has an extraordinary

affinity for combination with pigment. It is more or less of the nature of a combination, and to a certain extent this fact resembles those described for oxalic acid, since the pigment not only combines with the uric acid, but it influences also the shape of the crystals. Oxalic acid in the urine crystallises in the form of needles and rhomboids; when pure it is in plates, and you understand that the nucleus, of at any rate oxalic stones, is a single large crystal, and one has definite experimental evidence that such a crystal can be obtained by adding proteid material to urine containing oxalic acid.

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